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Epidemiology and patient burden of human parainfluenza virus in adults: a systematic review

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BACKGROUND

- Parainfluenza virus (PIV) is a single-stranded RNA virus of the paramyxoviridae family with 4 known serotypes (PIV1-4), each exhibiting distinct seasonality and geographic circulation patterns[1,2]
- PIV infection typically causes mild respiratory symptoms in the upper respiratory tract, though more severe infections can spread to the lower airways and cause complications such as pneumonia[3,4]
  - Of the serotypes, PIV3 infection is most often associated with clinically significant infections [4]
- PIV infection can be severe and is associated with high mortality in high-risk populations, such as in the elderly or the immunocompromised[1,2,4,5]
- Outbreaks of PIV can be difficult to control due to viral shedding in asymptomatic individuals, with outbreaks occurring within households, inpatient or outpatient facilities, nursing homes, and daycares [3]
- Infection often presents with cold-like symptoms in adults, including cough, rhinorrhea, and sore throat, which can be difficult to distinguish from other respiratory infections, contributing to a lack of epidemiological data in otherwise healthy (ie, not high-risk) adults[4]
- The lack of epidemiological data on PIV infection has subsequently led to scarce data on its disease burden in adults[1,2,4]
- To address these gaps, the objective of this systematic review was to evaluate the scope of published epidemiological and patient outcomes data available for PIV in adults worldwide and to identify data gaps for this patient population

METHODS

Search criteria

- PubMed was searched for original articles on epidemiology or patient outcome of PIV (any strain) published from January 1, 2014 to August 26, 2023
- Study inclusion criteria:
  - Participants included adults ≥18 years of age (studies with multiple age groups were retained but only data for those ≥18 years was included)
  - Assessed the prevalence or positivity rate of any PIV strain and/or burden of disease associated with any PIV strain
  - Study start date on or after 2014 (includes studies that may have started before but ended after 2014)
  - Sample size of interest ≥20
- Study exclusion criteria:
  - Review paper or meta-analysis
  - Lack of relevance (eg, not an epidemiology study, other virus studied/no PIV data, phylogeny study, single case study, animal or in vitro study)
  - Prevalence could not be calculated or determined, and there were no other data of interest
  - Primary time frame overlapped with the peak of the COVID-19 pandemic (2020-2022); studies with some overlap were included if the majority of the study was performed outside this window
- Bibliographies of excluded reviews were also examined to identify any studies not captured by the initial literature search
- Studies were screened for relevant data in adults and in those at high risk for respiratory infections (severe pulmonary diseases, malignancies, transplants, cystic fibrosis, or those who were unhoused)

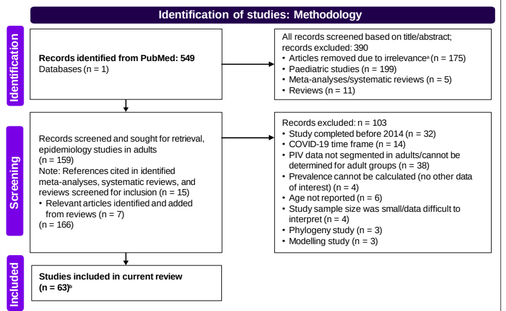
Data extraction

- All identified articles were reviewed and evaluated independently by a minimum of 2 researchers
- The following data were extracted from the final reference set:
  - Study design data: Authors, study time frame/design, country and location, study population (high-risk or low-risk; reasons for high-risk classification), age and age group (adults, older adults, or elderly adults), sample size
  - Epidemiological data: PIV strain, PIV prevalence and/or positivity rate (manually calculated in some cases), presence of coinfection
  - PIV-related burden data: burden outcomes
    - Progression from URTI to LRTI, rate of severe pneumonia, ED visits, outpatient visits, nursing visits, hospitalisation rate, length of stay, ICU admission, need for mechanical ventilation, need for oxygen, mortality, HCRU, quality of life measures

RESULTS

- The PubMed search identified 549 publications (**Figure 1**)
- 390 articles were excluded based on an initial screen of the title/abstract, yielding 166 articles for full text review
- This included 7 studies identified by screening bibliographies of excluded review articles that were not captured by the initial search
- Upon review, 103 further articles were excluded (see **Figure 1**)
- Taken together, this process identified a final database of 63 articles to analyze for reported epidemiological or outcome data

Figure 1: PRISMA flowchart of systematic review methodology

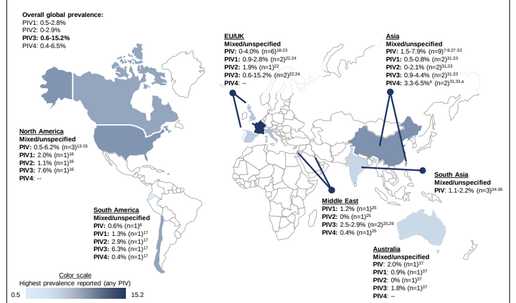


[a]Irrelevance: Not an epidemiology study, other virus studied or no PIV data, phylogeny study, single case study, animal or in vitro study, outside of time frame, or within COVID-19 time frame. [b]Includes studies that report PIV strain positivity rate out of PIV-positive samples, which differs from prevalence of PIV.

Prevalence

- The prevalence of PIV was highly variable based on geographic region and patient population (**Figure 2**), which included hospitalised adults, volunteer participants in surveillance programs, and those already testing positive for a respiratory virus
  - Most patients were symptomatic or had respiratory symptoms warranting a healthcare visit/testing with confirmed or suspected infection
- Overall prevalence of PIV (all strains) ranged from 0-15.2% (median 2%) in otherwise healthy adults (not high-risk but tested for infection) (**Figure 2**)
- Prevalence was generally higher in adults ≥65[6-10]
- The prevalence of PIV in high-risk adults was markedly higher than in otherwise healthy adults, with prevalences up to 41% in certain risk groups (transplant recipients)[11,12]

Figure 2: Published regional prevalence of PIV



Prevalence of PIV reported in previously published studies (2014−2023) is plotted by broad geographic region. Prevalence was defined as the percentage of detected PIV infections (any strain) out of all samples tested from the respective population, inclusive of hospitalised adults, surveillance data, or those already testing positive for a respiratory virus. In some cases, prevalence rates included here were manually calculated or pooled across multiple age groups from statistical data reported in the published sample set. N denotes the number of studies contributing to the listed range of PIV prevalence, by region. Countries with data available are color coded and scaled based on the highest prevalence reported for that region for any strain of PIV (see inset on bottom left). Countries lacking data are coded in white.

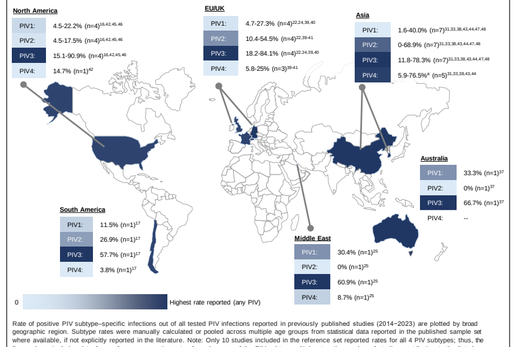
[a]Upper limit includes prevalence calculated based on reported rates for PIV4a and PIV4b combined.

- PIV3 was the most prevalent strain out of reported tested samples (0.6-15.2% [median 2.9]), followed by:
  - PIV4 (0.4-6.5% [1.9]), PIV1 (0.5-2.8% [1.1]), and PIV2 (0-2.9% [1.1])

Positivity rate

- The subtype positivity rate (PIV strain-specific positive samples out of all PIV-positive samples, as opposed to prevalence of the overall tested sample population) was also extracted from the reference set (**Figure 3**)
  - PIV3 was the most dominant subtype out of PIV-positive samples as well, with a positivity rate of 11.8-79.1%[17,25,33,38-40]
  - Only 10 studies tested for all 4 PIV subtypes, highlighting a need for additional testing of specific PIV strains
    - Despite PIV4 being the least frequently investigated strain,[4] positivity rates for PIV4 were high, suggesting PIV4 should be included in multiplex assays[17,25,31,38-44]

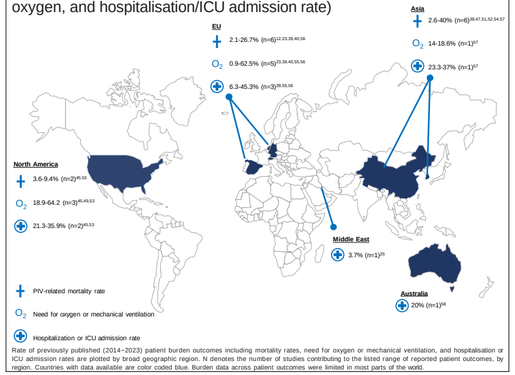
Figure 3: Published regional positivity rate of PIV subtypes out of total PIV infections



Rate of positive PIV subtype–specific infections out of all tested PIV infections reported in previously published studies (2014−2023) are plotted by broad geographic region. Subtype rates were manually calculated or pooled across multiple age groups from statistical data reported in the published sample set where available, if not explicitly reported in the literature. Note: Only 10 studies included in the reference set reported rates for all 4 PIV subtypes; thus, the figure above includes data from references reporting rates for only some of the PIV subtypes. N denotes the number of studies contributing to the listed range of PIV subtype rates, by region. Countries with data available are color coded, with countries lacking data within the sample set coded in blue. The highest reported rate for each strain is color coded and scaled per region (see inset on bottom left), with PIV3 being the most commonly detected PIV infection subtype in most regions, with the exception of Asia, where PIV3 and PIV4 were reported at similar peak detection rates.

[a]Range includes 1 study reporting specific rates for PIV4a and PIV4b.

Figure 4: Published regional burden of PIV infection (mortality, need for oxygen, and hospitalisation/ICU admission rate)



Rate of previously published (2014−2023) patient burden outcomes including mortality rates, need for oxygen or mechanical ventilation, and hospitalisation or ICU admission rates are plotted by broad geographic region. N denotes the number of studies contributing to the listed range of reported patient outcomes, by region. Countries with data available are color coded blue. Burden data across patient outcomes were limited in most parts of the world.

Burden/outcome data

- Patient outcome data were scarce, with mortality rates being the most frequently reported topic[38,49] (**Figure 4**)
  - Mortality rate for high-risk patients:
    - HSCT patients: 2−40%[12,38,39,47]
    - Oncology patients: 8−21%[38,40,50-52]
    - Lung transplant patients: 9%[53]
    - AECOPD: 3%[54]
- There was no clear strain-specific pattern of mortality given the limited data on patient outcomes
- The range of high-risk patients requiring either supplemental oxygen or mechanical ventilation was 0.9-64%[40,49]
- High-risk patients were hospitalised at a rate of 36−45%[39,53,55]
  - ICU admission rates in PIV-infected patients were 3.7−28%[25,56]
  - There was no clear geographic, strain-specific, or population-specific pattern of hospitalisation or ICU admission rates (**Figure 4**)
- There were no data on HCRU reported within this sample set

LIMITATIONS

- A single database was used to compile the reference set (PubMed)[6-68]
- The scope may have been impacted by the COVID-19 pandemic, as studies during the pandemic were removed over concerns that the epidemiological data reported were affected by social measures in place at the time
- Interpretation of available data is inherently limited by the high variability of study design, data stratification methods, and patient populations included in the compiled studies
  - In particular, the definitions of “prevalence” and “positivity rate” were highly variable across studies, contributing to the wide range of prevalence/positivity rates depending on the population whole

CONCLUSIONS

This systematic review compiled global epidemiologic and disease burden data for PIV in adults from 63 articles identified based on pre-determined search criteria

The prevalence of PIV was generally higher in high-risk patients and those ≥65 years

Significant knowledge gaps remain on the global burden of PIV, particularly regarding a complete lack of HCRU data in otherwise healthy adults

There is a need for prospective studies tracking clear delineated outcomes across PIV strains to better identify patterns of infection and patient outcomes

A vaccine or other preventive treatment for PIV targeting any or all serotypes would be beneficial given the risk for mortality or complications from PIV, particularly in HSCT/oncology patients or those with comorbidities at-risk for respiratory exacerbation

ABBREVIATIONS

AECOPD, acute exacerbations of chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ED, emergency department; HCRU, healthcare resource utilisation; HSCT, haematopoietic stem cell transplant; ICU, intensive care unit; LRTI, lower respiratory tract infection; PIV, parainfluenza virus; URTI, upper respiratory tract infection.

DISCLOSURES

- Oliver Martyn, Clemens Vlasich, and Rolf Kramer are employees of and may own shares/hold stock options in Sanofi.
- Peter JM Openshaw has received grants/research support from Medical Research Council UK, including joint awards with GSK (EMINENT consortium and INFLAMMAGE programme); UKRI MRC COVID-19 Rapid Response award; NIHR Senior Investigator Ref: NIHR201385; Coronavirus Clinical Characterisation Consortium (ISARIC-4C); and Innovative Medicines Initiative (IMI-2 Grant number 116019). He has received honoraria or consultation fees from Moderna, Janssen, Pfizer, GSK, Seqirus, AstraZeneca, Sanofi, and Icosavax and participated in company-sponsored speakers bureaus for Medscape, AstraZeneca, and Sanofi.

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REFERENCES

References are available on the electronic version by scanning QR code

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REFERENCES

1. Henrickson KJ. *Clin Microbiol Rev*. 2003;16:242-64.
2. Hall CB. *N Engl J Med*. 2001;344:1917-28.
3. Branche AR, Falsey AR. *Semin Respir Crit Care Med*. 2016;37:538-54.
4. Russell E, Ison MG. *Clin Infect Dis*. 2017;65:1570-6.
5. van Asten L, et al. *J Infect Dis*. 2012;206:628-39.
6. Caini S, et al. *J Infect Public Health*. 2019;12:357-63.
7. Dai Y, et al. *J Med Virol*. 2022;94:4369-77.
8. Li X, et al. *J Med Virol*. 2018;90:828-35.
9. Liu GS, et al. *Biomed Environ Sci*. 2019;32:438-45.
10. Price OH, et al. *Epidemiol Infect*. 2019;147:e221.
11. Helanterä I, et al. *Am J Transplant*. 2017;17:809-12.
12. Piñana J, et al. *J Infect*. 2020;80:333-41.
13. Lee N, et al. *CMAJ*. 2021;193:E439-E46.
14. Semret M, et al. *J Infect Dis*. 2017;216:936-44.
15. Shorr AF, et al. *Chest*. 2018;154:84-90.
16. Mandelia Y, et al. *Clin Microbiol Infect*. 2021;27:631.e1-.e6.
17. Saldías Peñafiel F, et al. *Rev Med Chil*. 2016;144:1513-22.
18. Bénézit F, et al. *Infection*. 2020;48:489-95.
19. Brendish NJ, et al. *Lancet Respir Med*. 2017;5:401-11.
20. Chasqueira MJ, et al. *Int J Infect Dis*. 2018;69:1-7.
21. De Francesco MA, et al. *Int J Environ Res Public Health*. 2021;18:9525.
22. Gadsby NJ, et al. *Clin Infect Dis*. 2016;62:817-23.
23. Recio R, et al. *J Med Virol*. 2021;93:4693-703.
24. Lemarie B, et al. *J Infect Dis*. 2022;226:1027-35.
25. Essa S, et al. *Virol J*. 2017;14:19.
26. Jornist I, et al. *J Clin Virol*. 2018;107:19-24.
27. Cui AL, et al. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2022;56:912-8.
28. Liu X, et al. *Int J Gen Med*. 2023;16:1671-9.
29. Qin S, et al. *J Clin Lab Anal*. 2020;34:e23419.
30. Tai CC, et al. *J Microbiol Immunol Infect*. 2021;54:858-64.
31. To KKW, et al. *Clin Microbiol Infect*. 2019;25:1539-45.
32. Zhou F, et al. *Eur Respir J*. 2019;54:1802406.
33. Li XQ, et al. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2017;48:891-4.
34. Anand M, Nimmala P. *Trop Med Int Health*. 2020;25:1503-9.
35. Bhardwaj S, et al. *Front Public Health*. 2022;10:936634.
36. Kumar R, et al. *J Glob Health*. 2021;11:04027.
37. Brestovac B, et al. *Respir Med*. 2020;161:105854.
38. Lee J, et al. *Ann Hematol*. 2020;99:1231-9.
39. Spahr Y, et al. *Open Forum Infect Dis*. 2018;5:ofy077.
40. Tabatabai J, et al. *PLoS One*. 2022;17:e0271756.
41. Chellapuri A, et al. *Influenza Other Respir Viruses*. 2022;16:1122-32.
42. DeGroote NP, et al. *J Clin Virol*. 2020;124:104261.
43. Fan ZW, et al. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2021;52:467-71.
44. Jang JG, et al. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1265-73.
45. Russell E, et al. *Clin Infect Dis*. 2019;68:298-305.
46. Sung AD, et al. *Clin Infect Dis*. 2016;63:999-1006.
47. Lee KH, et al. *J Microbiol Immunol Infect*. 2021;54:253-60.
48. Oh EJ, et al. *Environ Sci Pollut Res Int*. 2021;28:10018-26.
49. Seo S, et al. *Haematologica*. 2017;102:1120-30.
50. Iglói Z, et al. *J Hosp Infect*. 2022;126:56-63.
51. Kim YJ, et al. *Infect Dis (Lond)*. 2019;51:502-9.
52. Lee J, et al. *PLoS One*. 2021;16:e0260741.
53. Permpalung N, et al. *Transplantation*. 2021;105:2625-31.
54. Choi J, et al. *Yonsei Med J*. 2019;60:216-22.
55. de Zwart AES, et al. *Am J Transplant*. 2020;20:3529-37.
56. Martin D, et al. *Diagn Microbiol Infect Dis*. 2021;99:115244.
57. Li LJ, et al. *Zhonghua Yi Xue Za Zhi*. 2020;100:2109-15.
58. Ryan S, et al. *Am J Infect Control*. 2017;45:203-5.
59. Zheng YX, et al. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2019;40:911-6. 1
60. Xu J, et al. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2021;55:931-7.
61. Nabeya D, et al. *Medicine (Baltimore)*. 2022;101:e30819.
62. Moret F, et al. *Infect Dis (Lond)*. 2021;53:274-80.
63. Peghin M, et al. *Clin Infect Dis*. 2019;69:1192-7.
64. Kan OK, et al. *Respir Investig*. 2022;60:129-36.
65. Chow EJ, et al. *Emerg Infect Dis*. 2022;28:2343-7.
66. Dai MY, et al. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2257-63.
67. Kim YJ, et al. *Blood Adv*. 2022;6:5307-16.
68. Nazareth R, et al. *BMC Pulm Med*. 2020;20:39.