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Systematic review of multi-organ post-acute sequelae of Respiratory Syncytial Virus (RSV), influenza, Chikugunya, Zika, Yellow Fever and dengue.

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Introduction

- RSV, influenza, chikungunya, Zika, Yellow Fever, and dengue carry significant global health burden[1,2,3,4,5,6].
- While the acute burden of six major viruses is well-known, the evidence on their long-term, multi-organ post-acute sequelae (PAS) is fragmented and lacks a comprehensive, comparative synthesis[7].
- The absence of a consolidated overview limits the development of targeted public health interventions, such as virus-specific follow-up pathways and vaccination strategies.
- This review aims to systematically compare the patterns, prevalence, and risks of multi-organ PAS across these six viruses to provide crucial epidemiological insights.

Methods

- A systematic search of PubMed, Embase, CINAHL, Scopus, Global Health, and Web of Science was conducted from date of inception to August 2025.
- Cohort studies reporting on PAS in patients with confirmed infections versus uninfected controls were included, while excluding secondary literature, case reports, systematic reviews, and studies of vaccinated or pre-disposed patients.
- Study characteristics and outcomes such as prevalence, incidence, relative risk, and all-cause mortality and hospitalisation were extracted.
- Dual-investigator approach for study selection, data extraction and risk of bias assessment via the ROBINS-E tool.
- Findings are from an ongoing systematic review. The search for Dengue includes full citation searching, which is currently in progress for the remaining viruses.

Results

- Of 935 retrieved title-abstracts from the databases, 22 studies were selected for inclusion; full citation for dengue yielded 14 studies, leading to a total of 36 included studies (**Figure 1**).
- The types of PAS ranged from multisystem, cardiovascular, respiratory, neuropsychiatric, musculoskeletal, gastrointestinal, and autoimmune to general PAS, such as fatigue.
- Dengue:
  - Associated with a significant risk of multi-organ PAS, with the highest risk in the first 3 months post-infection.
  - Most commonly reported sequelae include psychiatric, autoimmune, and cardiovascular complications.
  - Subgroup analyses reveal distinct risks: females may have a higher risk of fatigue and stroke, males a higher risk of dementia, and children a higher risk of gastrointestinal complications.

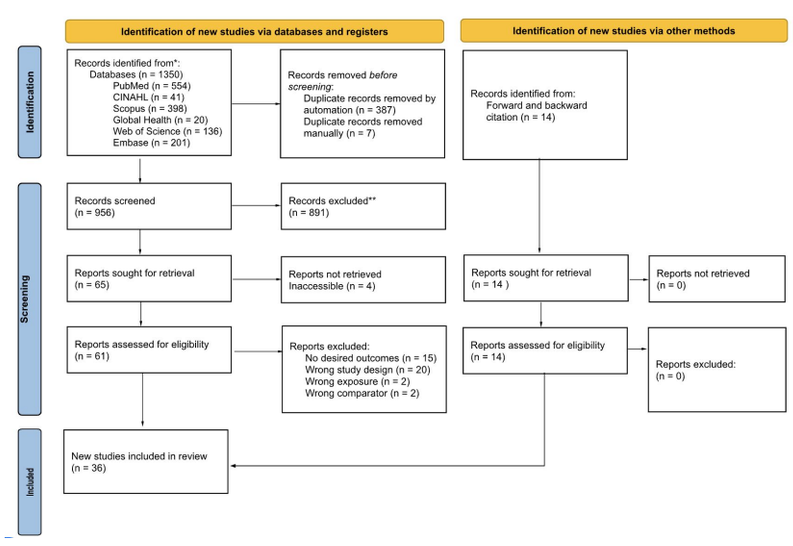

Figure 1: PRISMA flowchart of study selection process.

- Influenza (Primarily Adults):
  - Associated with a broad range of persistent general symptoms, with fatigue (18%) and joint pain (20%) being the most prevalent at 4 weeks.
  - Carries a markedly elevated risk of major thrombotic events that, while highest in the acute phase, persists for many months.
  - Overall risk of any PAS appears to be lower than that of COVID-19.
- RSV:
  - Strongly predictive of long-term paediatric respiratory morbidity, conferring an approximately 2.5-fold higher risk of subsequent respiratory issues compared to influenza.
  - Associated with a higher overall risk of any new diagnosis compared to both influenza and COVID-19 in paediatric cohorts.
  - Emerging evidence suggests an underrecognized risk of significant cardiovascular (aHR ≈ 1.6) and neurological (aHR ≈ 1.9) PAS in adults compared to COVID-19.
- Chikungunya, Zika & Yellow Fever:
  - This is a large, ongoing systematic review. The comprehensive search for these pathogens is complete, and full data extraction and synthesis to characterize their unique PAS signatures and determine the extent of the available evidence is underway.

Discussion

- This review shifts the perception of these viruses from acute illnesses to conditions with chronic manifestations and significant healthcare burdens.
- These findings underscore the need for pathogen-specific clinical follow-up, such as increased vigilance for thrombotic risk post-influenza[8] and a lower threshold for asthma investigation in children with a history of severe RSV[9].
- The evidence highlights the potential value of vaccination not only to prevent acute illness but also to mitigate the risk of significant long-term morbidity.
- Future research should prioritize mechanistic studies to understand these different viral pathways and address the critical evidence gaps, such as PAS of RSV in adults.

References

1. Troeger CE, Blacker BF, Khalil IA, Zimsen SR, Albertson SB, Abate D, Abdela J, Adhikari TB, Aghayan SA, Agrawal S, Ahmadi A. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. The Lancet respiratory medicine. 2019 Jan 1;7(1):69-89.
2. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, Madhi SA, Omer SB, Simões EA, Campbell H, Pariente AB. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. The Lancet. 2022 May 28;399(10340):2047-64.
3. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, Drake JM, Brownstein JS, Hoen AG, Sankoh O, Myers MF. The global distribution and burden of dengue. Nature. 2013 Apr 25;496(7446):504-7.
4. Tsetsarkin KA, Chen R, Sherman MB, Weaver SC. Chikungunya virus: evolution and genetic determinants of emergence. Current opinion in virology. 2011 Oct 1;1(4):310-7.
5. Puntasecca CJ, King CH, LaBeaud AD. Measuring the global burden of chikungunya and Zika viruses: A systematic review. PLoS neglected tropical diseases. 2021 Mar 4;15(3):e0009055.
6. Gaythorpe KA, Hamlet A, Jean K, Garkauskas Ramos D, Cibrelus L, Garske T, Ferguson N. The global burden of yellow fever. Elife. 2021 Mar 16;10:e64670.
7. Wee LE, Ho RW, Lim JT, Chiew CJ, Young B, Yung CF, Chong CY, Lye DC, Tan KB. Long-term sequelae post-hospitalization for respiratory syncytial virus vs. Omicron SARS-CoV-2 or influenza in adults and children: a retrospective cohort study. Clinical Microbiology and Infection. 2025 Apr 26.
8. Keene S, Abbasizanjani H, Torabi F, Knight R, Walker V, Raffetti E, Cezard G, Ip S, Sampri A, Bolton T, Denholm R. Risks of major arterial and venous thrombotic diseases after hospitalisation for influenza, pneumonia, and COVID-19: A population-wide cohort in 2.6 million people in Wales. Thrombosis Research. 2025 Jan 1;245:109213.
9. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. BMC pediatrics. 2013 Jun 19;13(1):97.