PEDIATRIC VIRAL INFECTION CONTROL: STRATEGIES FOR PREVENTION AND LONG-TERM SEQUELAE

Ph.D. Thesis Booklet

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1. Introduction

1.1. What is the topic?

Respiratory viral infections pose a significant global health burden, resulting in substantial morbidity, mortality, and economic impact worldwide, especially for risk populations, such as young children and those with comorbidities. While most viral respiratory infections are self-limiting, severe acute disease and long-term sequelae have long been recognized for pathogens such as influenza, respiratory syncytial, and coronaviruses, occasionally leading to persistent pulmonary and/or extrapulmonary sequelae that affect multiple organ systems, resulting in prolonged functional impairment and reduced quality of life.

2. What is the problem to solve?

2.1. Influenza vaccination

Seasonal influenza causes annual epidemics of varying severity and can result in serious complications in children and other vulnerable populations. Due to the continuous antigenic drift of influenza viruses and waning immunity,

the annual reformulation of vaccination, the cornerstone of prevention, is necessary. Strategies for immunization differ by composition, formulation, and route of administration, with live attenuated intranasal vaccines (LAIV) offering needle-free delivery and potentially higher acceptability. However, its use varies widely across countries due to its restricted accessibility, higher costs, and contraindications. Regarding vaccine valency, recent policy shifts have returned to trivalent formulations from quadrivalent ones, which contain the two A and only one B influenza strains. Before our study, comprehensive evidence synthesis evaluating direct comparative pediatric effectiveness, safety, and cost-effectiveness was scarce.

2.2. SARS-CoV-2 and Long COVID

In early 2021, knowledge about the long-term consequences of SARS-CoV-2 infection in children was scarce and largely extrapolated from adult studies. Early reports relied on heterogeneous case definitions, short follow-up, and inconsistent outcome measures, resulting in widely variable prevalence estimates and symptom

profiles. Although the NICE guideline provided early structured definitions, their applicability to children remained uncertain, and pediatric-specific clinical case definitions were only established later by the WHO. Available studies frequently lacked systematic clinical assessment or laboratory confirmation of acute infection, and often examined organ systems in isolation. Consequently, clinically grounded data were needed to better characterize the natural history and spectrum of pediatric long COVID, supporting the development of evidence-based care pathways.

3. What is the importance of the topic?

3.1. Influenza vaccination

Equally effective and safe pain-free vaccination options may improve acceptance, increasing coverage rates of pediatric influenza vaccination. As children play a central role in the transmission of respiratory viruses, increased uptake in this age group could yield substantial population-level benefits by reducing disease burden and protecting vulnerable groups.

3.2. Long COVID

Pediatric long COVID is an emerging public health concern, as persistent symptoms following even mild infections affect a significant proportion of children and impose substantial long-term burdens on physical functioning, cognition, school participation, psychosocial well-being, and healthcare systems.

3.3. What would be the impact of our research results?

Our comparative data, which support the optimization of pediatric influenza vaccination strategies, may increase uptake and population-level protection.

Pediatric clinical data on long COVID aids the development of evidence-based management pathways for post-viral sequelae.

4. Objectives

4.1. Study I. – Head-to-head comparison of influenza vaccines in children: a systematic review and meta-analysis

We aimed to evaluate the comparative effectiveness, safety, and cost-effectiveness of LAIV relative to inactivated influenza vaccines (IIV) in pediatric populations by synthesizing current evidence.

4.2. Study II. – Clinical assessment of children with long COVID syndrome

We decided to investigate the clinical characteristics and symptom patterns associated with pediatric long COVID in an observational cohort.

5. Methods

5.1. Study I. – Influenza vaccination

A systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines. The protocol was preregistered in PROSPERO (CRD42021285412), with minor deviations implemented to improve clinical relevance, including extension of the eligible age range to 21 years and supplementation of outcomes from clinical trial registries. Studies using mono- or bivalent vaccines were excluded, as these are no longer in contemporary use. Randomized, active-controlled trials directly comparing LAIV with IIV in pediatric or adolescent

populations were eligible for inclusion. Studies were required to report at least one of the following outcomes: laboratory-confirmed influenza infection, safety or reactogenicity events, or numerical cost-effectiveness data.

A comprehensive literature search was conducted in MEDLINE (PubMed), Embase, and the Cochrane Central Register of Controlled Trials, with the final update on November 13, 2023. Two reviewers independently screened records and extracted data, with disagreements resolved by consensus. The risk of bias was assessed using the Cochrane RoB 2 tool, and the certainty of evidence was evaluated using the GRADE framework. Pooled effect estimates were calculated as odds ratios with 95% confidence intervals using the random-effects Mantel–Haenszel method. Heterogeneity was assessed using the I^2 statistic, and sensitivity analyses included leave-one-out procedures. Subgroup analyses were performed by vaccine valency, study size, and age group. Analyses were conducted in R using the meta package.

5.2. Study II – Long COVID

A single-center, observational case series was conducted among children and adolescents attending a dedicated pediatric long COVID outpatient clinic at the Bókay Street Unit of the Pediatric Center, Semmelweis University (Budapest, Hungary). Data were collected between March and May 2021. Ethical approval was obtained, informed consent and age-appropriate assent were provided. Eligible participants had laboratory-confirmed SARS-CoV-2 infection at least one month prior to persistent symptoms consistent with the NICE case definition of long COVID. The study was descriptive in nature and did not include a control group. Clinical data were recorded using a standardized case report form that incorporated medical history, physical examination, laboratory and imaging results, specialist consultations, and a structured symptom questionnaire adapted from the World Health Organization's Post COVID-19 case report form. Symptoms were grouped into organ-system categories. Quality of life in terms of functioning (QoL-F) was assessed by 12 items on a 5-point scale from “no difficulty” to “extreme difficulty/cannot do”. Each item was also rated relative to the pre-COVID period on a

three-level scale (“better/same/worse”). Responses were summarized into two index scores (QoL-F and change in QoL-F), scaled from 0 to 100 while accounting for missing answers (QoL-F: 0 is “no difficulty”, 100 is “extreme difficulty”; QoL-F change: 0 is “better”, 50 is “unchanged”, and 100 is “worse”). Descriptive statistics were used to summarize clinical characteristics and symptom patterns. Associations were explored using an independent samples t-test with Hedges’ g effect size, confidence intervals, and Pearson’s correlation. Statistical analyses were performed using IBM SPSS Statistics.

6. Results

6.1. Study I. – Influenza vaccination

Out of the relevant 3,646 records, 22 randomized trials were included in the systematic review and 19 in the meta-analysis. Most trials compared trivalent LAIV and IIV, while no pediatric RCT directly compared the efficacy of quadrivalent LAIV with quadrivalent IIV. For laboratory-confirmed influenza, the pooled trivalent estimate showed no statistically significant difference between

LAIV and IIV (OR 0.77; 95% CI 0.44–1.34; 15,156 children), with low certainty of evidence. No individual study had a significant impact on the pooled estimates. The subgroup analysis of large multicenter trials showed that LAIV was significantly associated with a lower risk of infection (OR 0.50; 95% CI 0.28–0.88), with a high certainty of evidence.

No vaccination-related deaths were reported across the 8958 vaccinated participants. Only 23 vaccine-related serious adverse events (SAEs) were reported among 17,092 recipients of trivalent vaccines. Odds ratios for vaccine-related SAEs did not differ significantly by vaccine type (trivalent: OR = 1.07, 95%CI = 0.70;1.62, quadrivalent: OR 0.92, 95%CI = 0.46;1.87). Across specific outcomes, nasal symptoms were significantly more frequent after LAIV (OR = 1.55, 95% CI = 1.30;1.86). Cost-effectiveness evidence (three modeling analyses based on previous RCT data) consistently favored LAIV, although a quantitative synthesis was not feasible due to the incomplete reporting of confidence intervals. The risk of bias was generally low for efficacy

outcomes, but highly variable for safety reporting. We found no evidence of publication bias.

6.2. Study II. – Long COVID

Eighty-nine children with laboratory-confirmed prior SARS-CoV-2 infection were included (mean age 11.4 ± 3.8 years), with a female predominance (63%) after a mostly mild or asymptomatic acute infection (94%). None had received SARS-CoV-2 vaccination at the time of their first visit. At first assessment, symptom duration ranged from 5 weeks to 9.3 months (mean ~4.5 months). Symptoms were continuously present since acute infection in 65%, while 25% developed symptoms weeks later (10% after >1 month). Children reported a high symptom burden (mean 12 symptoms across ~5 organ systems). Fatigue was the most common symptom (70%), followed by neurocognitive, mood-related, vestibular, sleep-related, and post-exertional complaints; smell/taste changes were reported in 28%.

Objective findings corresponding to complaints were identified in a minority of cases; overall, 18% of symptoms matched symptom-concordant medical

findings. Pulmonary work-up had the highest diagnostic yield (abnormal lung function tests in 46% of those tested, largely obstructive patterns), while cardiology evaluations detected abnormalities in 15% of assessed children. Gastrointestinal investigations revealed abnormalities in 15% of symptomatic children (e.g., lactose intolerance, dysbiosis, hepatic steatosis), and dermatology consultations were positive in 63% of those assessed. Ultrasound confirmed autoimmune thyroiditis in 7% of cases.

Functioning was frequently affected. Among children with sufficient questionnaire data (n = 67), mean scores indicated mostly mild limitations (mean 27.1, *SD* = 22.8, min-max: 0-90.9). However, a comparison between pre- and post-COVID scores suggested an overall worsening (mean change 70.4, SD = 16.3, min-max: 45.8-100). Twenty-six % showed moderate-to-severe functioning impairment with a clear decline compared to the pre-COVID era. Self-care was assessed separately: among 73 respondents, 29% reported problems. Females experienced more symptoms and had longer symptom

durations than males. Older age was also correlated with longer long COVID symptom durations ($r = 0.58$, $p < 0.001$). Complaint co-occurrence mapping suggested clustering of general, neurologic, mental health, gastrointestinal, and cardiopulmonary complaints. Compared to the acute phase, during their long COVID phase, children experienced more mental health (73% vs. 17%), and cardiovascular symptoms (65% vs. 20%), while general (88% vs 83%) and neurological symptoms (85% vs. 77%) remained prominent.

7. Conclusions

Taken together, our results emphasize the need for an integrated approach to pediatric infectious disease control that combines optimized preventive interventions with structured strategies for recognizing and managing long-term post-infectious sequelae.

7.1. Study I. – Influenza vaccination

Both trivalent LAIV and IIV are efficacious and safe in pediatric populations. Given the needle-free administration of LAIV and its higher acceptability, its use should be actively supported in appropriate pediatric

settings, as increased uptake may enhance herd immunity and yield population-level and cost-related benefits.

7.2. Study II. – Long COVID

In the absence of reliable biomarkers or targeted therapies, health policies must ensure equitable access to comprehensive pediatric long COVID services, as many affected children experience substantial functional and mental health impairment despite limited objective clinical findings. At the same time, potential increases in autoimmune disease prevalence highlight the need for ongoing surveillance and focused research.

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