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DOKTORI ISKOLA

Ph.D. értekezések

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Gyermekkori betegségek klinikuma, élettana és prevenciója

című program

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

Ph.D. Thesis

Translational Medicine Program

Pharmaceutical Sciences and Health Technologies Division

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Budapest

2026

“Discovery consists of seeing what everybody has seen and thinking what nobody has thought.”

Albert Szent-Györgyi

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ATG	Anti-Thyroglobulin Antibody
ATPO	Anti-Thyroid Peroxidase Antibody
BNP	B-Type Natriuretic Peptide
CAR	Cardiological
CI	Confidence Interval
CENTRAL	Cochrane Central Register of Controlled Trials
COVID-19	Coronavirus Disease·2019
CRF	Case Report Form
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DER	Dermatologic
ECG	Electrocardiogram
EEG	Electroencephalogram
ENT-O	Ear–Nose–Throat and Ophthalmology
GEN	General
GIS	Gastrointestinal
GRADE	Grading of Recommendations Assessment Development and Evaluation
I^2	Higgins' Heterogeneity·Statistic
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIV	Inactivated Influenza Vaccine
IL-6	Interleukin-6
LAIV	Live Attenuated Influenza Vaccine
LDH	Lactate Dehydrogenase
MEDLINE	Medical Literature Analysis and Retrieval System Online
MIN	Minimum
MAX	Maximum
MRI	Magnetic Resonance Imaging

MUS	Musculoskeletal
NEU	Neurologic
NICE	National Institute for Health and Care Excellence
NT-pro-BNP	N-Terminal Pro-B-Type Natriuretic Peptide
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QoL-F	Quality of Life – Functioning
REP	Reproductive
RCT	Randomized Controlled Trial
RoB2	Revised Cochrane Risk-of-Bias Tool for Randomized Trials
PUL	Pulmonary
PSY	Psychological
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus·2
SD	Standard Deviation
TRAK	Thyroid Stimulating Hormone Receptor Antibody
TSH	Thyroid Stimulating Hormone
US	Ultrasound
USA	United States of America
WHO	World Health Organization
6mWT	Six-Minute Walking Test
τ^2	Between-study variance

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to contribute to evidence-based pediatric care that is child- and family-friendly, responsive to the complexity of childhood illnesses. I aim to support preventive strategies and clinical management pathways that are not only clinically effective and safe, but also accessible and acceptable for children and families.

My mission was to generate robust comparative evidence that informs pediatric influenza vaccination strategies and to advance structured, science-based approaches to post-viral care in children. Shaped by clinical experience with pediatric long COVID, my work is guided by an integrative perspective that considers both physical and psychological aspects of health, valuing creative, systems-level thinking in addressing complex clinical problems.

Scientometrics

Number of all publications:	7
Cumulative IF:	30.6
Av IF/publication:	4.37
Ranking (SCImago):	D1:5, Q1:2
Number of publications related to the subject of the thesis:	2
Cumulative IF:	10.6
Av IF/publication:	5.3
Ranking (Sci Mago):	D1:2
Number of citations on Google Scholar:	57
Number of citations on MTMT (independent):	33
H-index:	5 (ResearchGate)

The student's detailed bibliography can be found on pages 68-69.

2.2. Future plans

In the coming years, I aim to shape further my clinical and research path at the intersection of pediatric care and prevention.

In the short term, we have obtained new ethical approval to investigate neutrophil alterations observed in children with long COVID, to assess their temporal dynamics and clinical relevance. This work reflects my intention to pursue both basic and clinical research, linking biological mechanisms to patient-level clinical findings. In parallel, I am actively involved in the development of a Hungarian national pediatric quality of life questionnaire, which aims to compare children living with chronic diseases with their healthy peers, representing a complementary clinical and patient-centered research direction.

I value collaborative work and enjoy contributing to supportive research environments. I am motivated by the idea that research can be both rigorous and creative, particularly when teams actively support one another's growth. For this reason, I hope that within the framework of the Semmelweis Pediatric Research and Innovation Group (SPRING), we can pursue ambitious goals together and help others experience the intellectual and human value of collaborative research.

3. SUMMARY OF THE THESIS

Pediatric viral infections challenge healthcare systems not only through acute disease but also through their long-term consequences. Young children and those with comorbidities are a high-risk group for severe deterioration. Children are key drivers of transmission and might develop post-infectious sequelae, making pediatric-focused evidence essential for effective infection control.

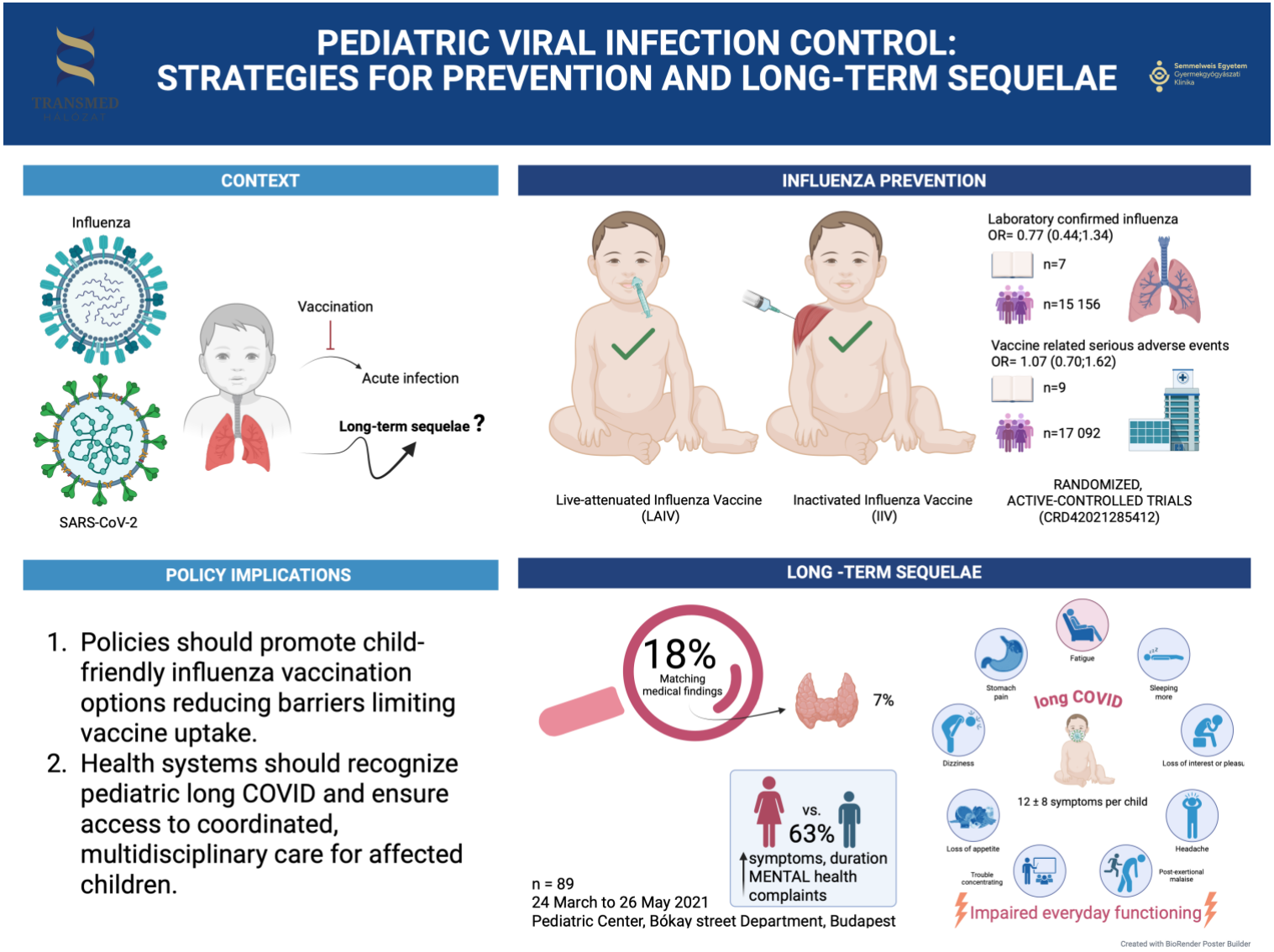
This thesis combines two research directions that have emerged from clinical practice: the optimization of preventive strategies for influenza and the structured clinical understanding of pediatric long COVID. While these topics address different stages of viral disease, they are linked by a shared aim to improve child-friendly, evidence-based care.

Our first study synthesizes randomized evidence comparing live attenuated intranasal (LAIV) and inactivated influenza vaccines (IIV) in children. The results demonstrate comparable overall effectiveness and favorable safety profiles. However, data from large clinical trials and economic models indicate the superiority of intranasal vaccination. The needle-free administration of LAIV is associated with higher acceptability among children, facilitating its integration into pediatric immunization programs, where increased uptake may translate into broader population-level benefits.

Our second study represents a cross-sectional clinical characterization of a new entity, referred to as pediatric long COVID. Despite predominantly mild acute SARS-CoV-2 infection, children experienced numerous persistent symptoms with substantial change in their functioning, while rates of objective clinical findings were limited. In the absence of reliable biomarkers or targeted therapies, these findings highlight the need for equitable access to comprehensive pediatric long COVID services. Furthermore, the identification of autoimmune conditions highlights the importance of ongoing surveillance and targeted research to understand long-term post-viral outcomes in children better.

Taken together, the results highlight the importance of integrating effective, child-friendly prevention strategies with structured, evidence-based approaches to recognizing and managing long-term sequelae in pediatric infectious diseases.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

Respiratory viral infections pose a significant global health burden, resulting in substantial morbidity, mortality, and economic impact worldwide (1,2). 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 affecting multiple organ systems, resulting in prolonged functional impairment and reduced quality of life (3–13).

This thesis investigates pediatric respiratory viral infections from two complementary perspectives. One part focuses on influenza immunization strategies, while the other addresses post-infectious sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), each contributing to pediatric healthcare from a different angle.

5.2. What is the problem to solve?

5.2.1. Influenza

Seasonal influenza causes annual epidemics of varying severity. While most infected individuals develop acute respiratory symptoms and recover within a week, influenza may cause severe or even fatal complications, particularly in vulnerable populations such as young children or individuals living with chronic diseases (8).

Waning host immunity and continuous antigenic drift of circulating influenza A and B viruses necessitate the annual reformulation of vaccines, which remains the primary preventive strategy (Table 1) (8,14). Although non-pharmaceutical public health interventions substantially altered influenza epidemiology during the SARS-CoV-2 pandemic (8,15,16), pediatric transmission remained relatively stable, according to U.S. data (17), underscoring the importance of immunization (8,14).

One key element of influenza vaccination strategy has been vaccine strain composition, which historically evolved toward quadrivalent formulations to broaden the protection by including both the two influenza B and A lineages (Table 1); however, regulatory agencies have recently recommended a return to trivalent formulations containing two A strains and a single B influenza lineage (18–20).

In addition to strain selection, influenza vaccination strategies in children differ according to formulation and route of administration (Table 1). LAIV offers several theoretical advantages, including needle-free delivery, ease of administration, and potentially higher acceptability (13,21–23). Nevertheless, its global availability varies widely, ranging from fully funded school-based programs to complete absence in many regions (13,24–27). Moreover, compared with IIV, the use of LAIV is considerably more restricted, and it is more expensive (Table 1) (8,28,29).

Prior to our work, existing evidence on pediatric vaccine performance was dominated by data from observational studies, demonstrating heterogeneous and geographically variable effectiveness, with limited distinction between pediatric and adult outcomes (30,31). Moreover, while efficacy against placebo has been demonstrated for trivalent influenza vaccines, suggesting that LAIV has superior efficacy, data on quadrivalent vaccines are controversial (20,31). Still, comparative evidence directly assessing their relative performance in pediatric populations is limited (30,31). Moreover, prior reviews lacked quadrivalent head-to-head randomized controlled trials and did not

comprehensively address safety or cost-effectiveness outcomes (32). Differences in accessibility, eligibility criteria, and associated costs, combined with the lack of robust comparative pediatric evidence, have contributed to substantial international variation in vaccination policies, funding structures, and coverage rates, which remain below the WHO's recommended 75% uptake (33–35). Thus, there is a need to support strategies that are not only effective and safe but also associated with higher acceptance.

Table 1. Influenza vaccine types for children (8,29,37,38)

	Inactivated influenza vaccine (IIV)	**Live-attenuated influenza vaccine (LAIV)**
Route of administration	Intramuscular or subcutaneous	Intranasal
Approved age range	≥6 months	2–17 years (Europe) / 2–49 years (USA)
Dosing schedule	<9 years (first vaccination): two doses ≥ 4 weeks apart ≥9 years: one dose annually	
Contraindications (might differ according to regions)(14,36)	History of anaphylaxis after a previous dose or vaccine component	History of anaphylaxis after a previous dose or vaccine component, Pregnancy, Immunosuppression (including close contacts of severely immunosuppressed individuals), Aspirin or salicylate use, Recent antiviral use (oseltamivir or zanamivir within 48 h; peramivir within 5 days; baloxavir within 17 days), Age 2–4 years with asthma diagnosis or wheezing in the previous 12 months, Active cerebrospinal fluid leak or oropharyngeal communication Cochlear implant, Anatomic or functional asplenia
Relative cost (approx.)	Lower ($6.49–$10)	Higher ($24–$29)

5.2.2. SARS-CoV-2 and Long COVID

At the initiation of our study in the early months of 2021, published evidence regarding the long-term effects of SARS-CoV-2 infection, commonly referred to as "long COVID," were limited. Available reports consisted mainly of anecdotal descriptions and small observational studies. These studies employed heterogeneous case definitions, had limited follow-up periods, and applied inconsistent outcome measures. Consequently, reported estimates of prevalence, symptom profiles, and risk factors varied widely and were affected by selection and ascertainment bias. At that time, frameworks and clinical guidelines were primarily derived from adult populations **(39–42)**.

The National Institute for Health and Care Excellence (NICE) guideline provided one of the earliest structured case definitions, distinguishing between different phases of COVID-19 (43,44). However, their applicability to pediatric populations remained uncertain. In the absence of a validated child-specific research case definition before 2022, and with a pediatric clinical case definition published by the World Health Organization only in 2023 (44,45), the umbrella term *"long COVID"* was commonly used to encompass both ongoing symptomatic COVID-19 and post-COVID-19 syndrome in children (Figure 1). **(43,44)**.

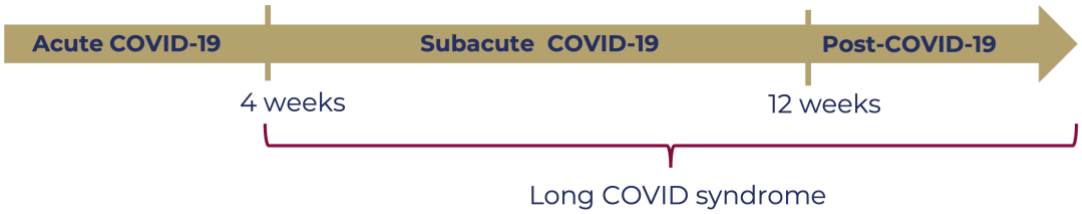


Figure 1. Case definitions of long-term consequences following COVID-19 according to the NICE guideline

The NICE guideline also outlined early approaches for identification, assessment, and management, emphasizing multidisciplinary care, exclusion of alternative diagnoses, and rehabilitation (43,44).

At the time our study was accepted for publication, available scientific data were still derived from studies often lacking comprehensive clinical characterization, standardized follow-up, or laboratory confirmation of acute infection **(45–47)**. Long-term outcomes affecting various organ systems were typically investigated separately, limiting an integrated understanding of the condition **(48–50)**. Given the absence of systematic pediatric-specific clinical knowledge on long COVID and the emerging evidence suggesting that long COVID may differ in children compared with adults (51), child-specific systematic clinical data were required to better define the natural history and clinical spectrum of pediatric long COVID and to support the development of evidence-based guidelines.

5.3. What is the importance of the topic?

5.3.1. Influenza

As children are key drivers of respiratory virus transmission, improving prevention among this age group has broad population-level benefits, including protection of other vulnerable subjects and a reduction in healthcare burden (52). To achieve such goals, we need to design cost-effective and highly acceptable, effective, and safe childhood vaccination programs; thus, understanding the comparative performance of available influenza vaccines is critical.

5.3.2. Long COVID

Pediatric long COVID represents a significant and emerging public health issue, as it has been estimated that approximately 10–20% of children may experience persistent symptoms following an otherwise mild acute infection. Given the large number of children infected worldwide, even a relatively low prevalence of post-acute symptoms corresponds to a substantial absolute burden for affected children, families, and health care systems, with effects likely to extend far beyond the immediate period. Persistent symptoms may interfere with physical functioning, cognitive performance, school attendance, psychosocial well-being, and overall quality of life during critical stages of development (53,54).

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

5.4.1. Impact on Influenza Prevention

In the context of insufficient vaccination coverage, options that may improve vaccine uptake, including pain-free administration methods, could provide substantial long-term benefits *(35,52)*. Thus, by synthesizing comparative evidence on influenza vaccination, this work provides policymakers with data relevant to optimizing pediatric vaccination strategies.

5.4.2. Impact on Long COVID Clinical Care

The pandemic presented an unprecedented opportunity to study post-viral syndromes on a large scale, enabling early and detailed clinical characterization of persistent symptoms following acute COVID-19. These findings can guide the development of structured assessment pathways and child-specific case definitions.

5.4.3. Impact on Policy

This work provides evidence relevant to future policymaking on both pediatric influenza vaccination strategies and organized post-viral care systems.

5.4.4. Impact on Future Research

The findings reveal important evidence gaps in pediatric long COVID and support hypothesis generation for future research, as well as provide methodological insights for future vaccine studies.

In summary, the combined findings may contribute to improved pediatric influenza protection programs and how we support those experiencing prolonged COVID-19-related symptoms, ultimately contributing to healthier childhoods and more resilient healthcare systems.

6. OBJECTIVES

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

The first study aimed to evaluate the comparative effectiveness, safety, and cost-effectiveness of LAIV relative to IIV in pediatric populations by synthesizing current evidence.

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

The second study investigated the clinical characteristics and symptom patterns associated with pediatric long COVID in an observational cohort.

7. METHODS

7.1. Study I. - Influenza vaccination

7.1.1. *Methodology and Protocol*

Our review was conducted in accordance with the PRISMA recommendations (55). The protocol was preregistered in PROSPERO (CRD42021285412), from which minor deviations were implemented to increase the clinical relevance and completeness of the dataset. Specifically, we expanded the eligible age range to 21 years and supplemented the dataset with outcomes retrieved from clinical trial registry sites. Additionally, we excluded studies that used mono- or bivalent vaccines, which are no longer in contemporary practice (14). Data on influenza-like illness were insufficient for analysis, and antibody response results were highly heterogeneous with limited real-world applicability (56).

7.1.2. *Eligibility Criteria*

We included randomized, active-controlled trials directly comparing LAIV with IIV in pediatric populations. Studies were eligible if they reported at least one of the following outcomes:

- rates of laboratory-confirmed influenza infection
- safety or reactogenicity events
- numerical cost-effectiveness data

In cases where multiple publications described overlapping datasets, peer-reviewed articles were prioritized.

7.1.3. Information Sources and Search Strategy

A comprehensive search was conducted in MEDLINE (via PubMed), Embase, and the Cochrane Register of Controlled Trials (CENTRAL). The final update occurred on 13 November 2023. The used search terms combined concepts of vaccination, influenza, pediatric population, and randomization, using both full keywords and truncations to maximize sensitivity. The reference lists of included papers and relevant reviews were also hand-searched.

7.1.4. Study Selection and Data Extraction

Two reviewers independently screened all records using Rayyan.ai (Rayyan Systems Inc., 2020). Following duplicate removal, title and abstract selection and full text retrieval took place in sequence. The agreement between reviewers was quantified using Cohen's Kappa at each stage, and disagreements were resolved through discussion.

Data extraction was carried out independently by two reviewers.

For each study, we collected information on:

- first author and year of publication
- study design, setting
- participant characteristics
- vaccine regimens
- data on eligible outcomes

7.1.5. Risk of Bias and Quality of Evidence Assessment

The risk of bias of the included randomized trials was evaluated using the Cochrane RoB 2 tool (RoB-2) (57). The certainty of evidence across outcomes was assessed using the GRADE approach (58). Two independent reviewers carried out both assessments. In the case of disagreements, a third reviewer decided them.

7.1.6. Data Synthesis and Analysis

Pooled effect estimates were calculated as odds ratios (ORs), with 95% confidence intervals (CIs), prediction intervals, and p-values using the random-effects Mantel-Haenszel method (59,60). For outcomes where studies with zero events were present, we applied a correction of 0.5 to the cell frequencies to calculate the individual OR. Pooled results were then estimated using the exact Mantel-Haenszel method. Between-study variance (τ^2) was estimated using the Paule-Mandel method with Hartung-Knapp adjustment (61,62). Heterogeneity was assessed using I^2 statistics and its confidence interval, and with the use of the Cohrane's Q test. Data visualizations were performed with forest plots and publication bias was examined using funnel plots (≥8 studies) and Egger's test (≥10 studies). Sensitivity analyses included leave-one-out procedures.

All analyses were performed in R (version 4.1.2.) using the meta package in line with Harrer et al. with the help of a professional statistician (32,63).

7.1.7. Subgroup analyses

To improve generalizability and to explore the hypothesis that pre-existing immunity and immunological maturation, and the number of added strains, may influence vaccine performance, we did subgroup analyses based on:

- vaccine valency
- study size
- age categories (64,65)

7.2. Study II. – Long COVID

7.2.1. Study Design

We reported on a single-center, observational case series of children and adolescents with long COVID syndrome who attended our dedicated outpatient clinic. The clinical work-up followed a diagnosis-by-exclusion approach, combining routine pediatric assessments with targeted, multidisciplinary investigations. The study was descriptive in nature and did not include a control group.

7.2.2. Study Setting

The study was conducted at the 1st Department of Pediatrics, now known as the Bókay street Unit of the Pediatric Center, Semmelweis University (Budapest, Hungary), where a specialized long COVID clinic for children was launched in March 2021. Data collection spanned from 24 March to 26 May 2021. Families from anywhere in the country could arrange appointments through an online booking system; no referral from a general practitioner or pre-screening was required.

7.2.3. Ethics and Patient Consent

The project was approved by the national medical research ethics committee (ETT TUKEB, approval number IV/5943 – 1/2021/EKU). All assessments were integrated into routine clinical care. Data were collected, anonymized, and analyzed collectively for research purposes. Parents provided informed consent for participation, and children contributed assent appropriate to their age.

7.2.4. Participants

All consecutive children presenting to the long COVID clinic during the study period were screened for eligibility. Case definition was based on the NICE guideline. They described long COVID syndrome based on compatible clinical or laboratory evidence of prior COVID-19 infection at least one month before the onset of current symptoms, which could not be better explained by an alternative diagnosis. Long COVID in this study encompassed both "ongoing symptomatic COVID-19" (4-12 weeks after acute disease) and "post-COVID-19 syndrome" (>12 weeks) (Figure 1) (43,44). Children with only clinically suspected, but not laboratory confirmed, acute infection were excluded to reduce misclassification.

7.2.5. Variables and Data Sources

Clinical information was recorded in a standardized case report form (CRF) that integrated:

- medical history
- physical examination
- results of laboratory, imaging, and electrophysiological studies
- specialist consultation reports

7.2.6. Questionnaires and symptom mapping

The CRF incorporated the WHO Post COVID case report form (66), which was translated and adapted to our local clinical needs. This tool covers:

- characteristics of the acute infection
- persisting new symptoms
- quality of life (functioning)

Before the first visit to the clinic, parents, together with their children, completed this online survey. The long COVID symptom module contained 50 items, which were later grouped into ten organ-system categories: general, cardiovascular, neurologic, mental health, gastrointestinal, dermatologic, musculoskeletal, pulmonary, ear-nose-throat and ophthalmologic (ENT-O), and reproductive. 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”).

7.2.6.1. Clinical and laboratory variables

In accordance with NICE recommendations, all children underwent:

- complete physical examination, and
- predefined panel of blood tests, including:
    - complete blood count,
    - basic clinical chemistry (electrolytes, liver and renal function markers, C-reactive protein (CRP), creatinine-kinase (CK), total protein, albumin, lactate-dehydrogenase (LDH), ferritin),
    - Il-6, BNP/NT-proBNP, D-dimer, troponin,
    - thyroid function and thyroid autoantibodies (TSH, free T3, T4, anti-thyreoperoxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-TG), TSH receptor antibody (TRAK),
    - SARS-CoV-2 IgM, IgG (spike)

Further diagnostic tests, such as imaging (e.g. chest X-ray, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), lung function testing, or specialists’ consultations were requested as guided by presenting symptoms and initial findings based on local guidelines.

7.2.7. *Standardized* definitions

Laboratory reference ranges were based on age-specific institutional pediatric norms.
Chronic medical conditions were defined using discharge diagnoses documented prior to or during the clinic visit. Obesity was characterized using national, age-specific body mass index (BMI) Z-score thresholds.

7.2.8. Bias, Confounding, and Evidence Synthesis

Several steps were taken to improve internal validity. First, only children with laboratory-confirmed SARS-CoV-2 infection were included, thereby reducing the risk of misclassification of exposure. Secondly, the questionnaire responses were reviewed and verified by the examining pediatrician, who also documented objective findings in the

CRF. Finally, data entry from CRFs into analysis datasets was checked and revalidated by the study team and our professional biostatistician.

As an observational case series without a control group, the study was not designed to make causal inferences. Therefore, we only performed a descriptive synthesis. Potential confounders, such as age, sex, and pre-existing conditions, were recorded for context but not adjusted for in the analysis, as no formal comparative analyses were planned.

7.2.9. Statistical Methods

Data from the CRFs were retrieved into data tables and checked for accuracy in collaboration with a professional biostatistician. Descriptive statistics were used to summarize continuous variables as means ± standard deviations (SD), or median and interquartile ranges (IQR). Categorical variables were presented as absolute counts and percentages (%). Group comparisons between continuous variables were made using independent samples t-tests with Hedges' g effect size, confidence intervals. Associations between continuous variables were examined using Pearson's correlation coefficient.

The significance level was set a priori at $\alpha = 0.05$. Statistical analyses were performed by our professional biostatistician using IBM SPSS Statistics, version 25.0, and network visualizations were generated with the qgraph package of R (version 1.6.9.).

8. RESULTS

8.1. Study I - Influenza

8.1.1. Study Search and Selection

The search identified a broad set of eligible trials (n= 3646). After eligibility assessment, 22 studies were included in the systematic review. The meta-analysis incorporated 19 studies, of which eight trials provided data on laboratory-confirmed influenza, and all of them reported on safety outcomes (Figure 2, Table 2).

The majority of the included studies evaluated trivalent formulations of both IIV and LAIV, while data on quadrivalent comparisons were scarce. Notably, no randomized trial compared quadrivalent vaccines. Only one small study contrasted quadrivalent LAIV with a trivalent injectable vaccine (67).

The included studies were highly heterogeneous, encompassing single-center to large multicenter trials conducted over multiple influenza seasons, enrolling participants from infancy through young adulthood (max. 21 years) and including both healthy children and those with a wide range of underlying medical conditions, across different vaccine formulations and study designs (Table 2).

The PRISMA diagram summarizing the screening process is presented in Figure 2 (32).

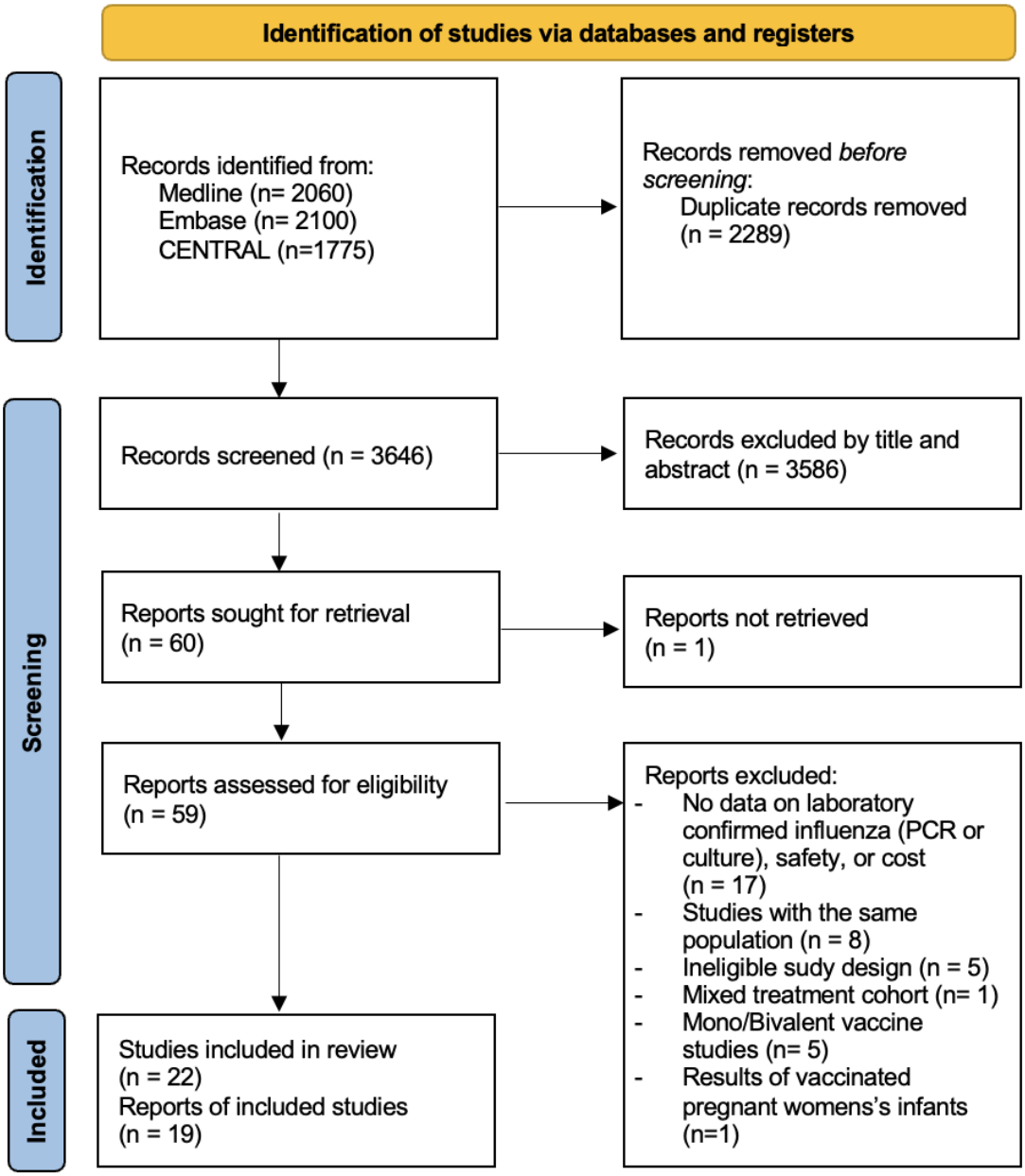


Figure 2. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review comparing live-attenuated and inactivated influenza vaccines in children (32)

Table 2. Basic characteristics of included studies (32)

Author (year)	Style	Number of centers	Study period	Mean age (range), in years	Health status	Treatments (dose)	Confirmed influenza (Number of children/ event number)	Safety outcomes
Ashkenazi et al. (2006) (68)	Individually radomized, open-label	>100 centers	2002-2003	3.0 (0.5-5.9)	Recurrent respiratory tract infections	TLAIV (2) TIV (2)	1050/29 1035/60	Related and overall serious adverse events, adverse events, hospitalization, subfebrility, fever, sore throat, cough, runny nose, otitis media, irritability, headache, decreased appetite, decreased activity, vomiting, muscle- or body ache, chills
Belshe et al. (2007) (69)	Individually randomized double-blind	>100 centers	2004-2005	(0.5-4.9)	Wheezer 6%	TLAIV (1-2[a]) TIV (1-2[a])	3916/153 3936/338	Related and overall adverse events, hospitalization, subfebrility, wheezing, runny nose
Carr et al. (2011) (70)	Cluster randomized open-label	<100 centers	2008-2009	10.4 (2.1-21.0)	Cancer	TLAIV (1-2[b]) TIV (2)	28/1 27/2	Related and overall serious adverse events, subfebrility, sore throat, cough, runny nose, irritability, headache, decreased activity, vomiting, muscle- or body ache, chills
Fleming et al. (2006) (71)	Individually randomized open-label	>100 centers	2002-2003	11.0 (6-17.9)	Asthma	TLAIV (1) TIV (1)	1111/50 1106/73	Related serious adverse events, adverse events, hospitalization, subfebrility, fever, sore throat, cough, runny nose, otitis media, irritability, headache, decreased appetite, decreased activity, vomiting, upper respiratory tract infections, nasopharyngitis, muscle- or body ache, chills, asthma attack
Hoft et al. (2011) (72)	Individually randomized open-label	<100 centers	2005-2006	(0.5-2.9)	Healthy	TLAIV (2) TIV (2)	Not included	Subfebrility, fever, runny nose
		<100 centers	2006-2007	(1.0-2.9)				
Ilyushina et al. (2015) (73)	Individually randomized open-label	<100 centers	2010-2012	5.4 (2.25-9.7)	Healthy	TLAIV (1-2) TIV (1-2)	13/0 18/0	Subfebrility, fever, upper respiratory tract infections
Krishnan et al. (2021) (74)	Individuallyrandomized triple-blind	<100 centers	2015-2017	(2.0-10.0)	Half of children is malnourished	TLAIV (1) TIV (1-2[b])	1087/279 1092/287	Related and overall serious adverse events, subfebrility, irritability, headache, decreased appetite, decreased activity, vomiting, diarrhea

Author (year)	Style	Number of centers	Study period	Mean age (range), in years	Health status	Treatments (dose)	Confirmed influenza (Number of children/ event number)	Safety outcomes
Kwong et al. (2015) (75)	Cluster randomized open-label	<100 centers	2013-2014	(4.0-14.0)	Children	TLAIV (1-2[b]) TIV (1-2[b])	Not included	Adverse events
Levin et al. (2008) (76)	Individually randomized open-label	<100 centers	2004-2005	(5.0-17.9)	HIV	TLAIV (1) TIV (1)	Not included	Skin reactions, nasopharyngitis, ear and eye reactions
Loeb et al. (2016) (77)	Cluster randomized double-blind	<100 centers	2012-2015	(3.0-15.0)	Healthy	TLAIV (1-2[b]) TIV (1-2[b])	1473/91 1201/77	Related serious adverse events, adverse events, hospitalization, subfebrility, sore throat, skin reactions, runny nose, headache, decreased appetite, vomiting, muscle- or body ache, ear and eye reactions, diarrhea, chills
Luce et al. (2008) (78)	Cost-effectiveness modeling study of data of the 2.0-4.9 years old cohort from the Belshe et al. (2007)[20] study.							
Neuzil et al. (2001) (79)	Individually randomized double -blind	<100 centers	1985-1990	(1.0-16.0)	Healthy	TLAIV (1) TIV (1)	Not included	Related and overall serious adverse events, subfebrility, sore throat, cough, runny nose
Smolen et al. (2014) (80)	Cost-effectiveness modeling study of data from the Ashkenazi et al. (2006)[32] and Fleming et al. (2006)[26] studies.							
Sokolow et al. (2022) (81)	Cluster randomized open-label	<100 centers	2018-2020	(5.0-17.0)	Asthma	QLAIV (1) QTIV (1)	Not included	Runny nose, sore throat, chills, ear and eye reactions, headache, muscle-or body ache, decreased activity, skin reactions, fever, wheezing, asthma attack, cough
Tarride et al. (2012) (82)	Cost-effectiveness modeling study of three age cohorts of Canadian children: 2.0–5.0 years of age, 6.0–9.0 years of age, and 10.0–17.0 years of age. Vaccine efficacy was taken from the Belshe et al. (2007) study[20].							
EU-CTR 2004-000585-13 (83)	Individually randomized double -blind	>100 centers	2004-2005	(0.5-4.9)	Healthy	TLAIV (1-2[a]) TIV (1-2[a])	Not included	Mortality, people affected by related serious adverse events, adverse events, skin reactions, otitis media, upper respiratory tract infections, nasopharyngitis, ear and eye reactions, diarrhea, asthma attack
NCT00461981 (84)	Individually randomized open-label	<100 centers	2007-2008	(1.0-2.9)	Healthy	TLAIV (2) TIV (2)	Not included	Related serious adverse events, adverse events, subfebrility, cough, runny nose, vomiting, upper respiratory tract infections, nasopharyngitis, diarrhoea
NCT01194297 (85)	Individually randomized open-label	<100 centers	2010-2011	(2.0-3.0)	Premature, very low birth weight	QLAIV (1) QIV (1)	Not included	Related and overall serious adverse events, adverse events

Author (year)	Style	Number of centers	Study period	Mean age (range), in years	Health status	Treatments (dose)	Confirmed influenza (Number of children/ event number)	Safety outcomes
					and former full-term infants			
NCT01246999 (86)	Individually randomized open-label	<100 centers	2010-2011	(3.0-9.0)	Healthy	TLAIV (2) TIV (2)	Not included	Related and overall serious adverse events, subfebrility, sore throat, wheezing, cough, runny nose, headache, decreased activity, muscle- or body ache
NCT02250274 (87)	Individually randomized open-label	<100 centers	2014-2015	10.0 vs.12.0[d] (5.0-17.0)	Healthy	QLAIV (1) TIV (1)	85/13 46/5	Related and overall serious adverse events
NCT03600428 (88)	Individually randomized open-label	<100 centers	2018-2020	(5.0-11.0)	Asthma	QLAIV (1) QIV (1)	Not included	Mortality, related and overall serious adverse events, wheezing, cough, asthma attack
NCT03982069 (89)	Individually randomized open-label	<100 centers	2019-2021	(4.0-21.0)	Healthy	QLAIV (1) QIV (1)	Not included	Mortality, related and overall serious adverse events, adverse events

TLAIV: trivalent live attenuated influenza vaccine; TIV: trivalent inactivated influenza vaccine; QLAIV: quadrivalent live attenuated influenza vaccine; QIV: quadrivalent inactivated influenza vaccine

[a]Second dose, if none before

[b]Second dose, if <9 years old, less than 2 prior vaccinations

[c]Second dose, if post-vaccination serum HAI titers against H1N1 and H3N2 ≤ 8 were revaccinated

[d]Mean age was 10 in the LAIV group, 12 in the TIV

8.1.2. Primary Outcome

8.1.2.1. Laboratory-confirmed influenza

Across trivalent comparisons, based on data of more than 15,000 participants, the overall pooled estimate showed no statistically significant difference between LAIV and IIV in preventing laboratory-confirmed influenza (OR 0.77; 95% CI 0.44-1.34) with low certainty of evidence (Figure 3). The leave-one-out sensitivity analysis revealed no significant studies. No child or adolescent RCT directly compared quadrivalent LAIV with quadrivalent IIV; the only study compared quadrivalent LAIV to trivalent IIV (Figure 3).

In the subgroup of large, multi-center trials, LAIV was associated with significantly lower odds of influenza infection compared with IIV (OR 0.50; 95% CI 0.28-0.88) with a high certainty of evidence. By contrast, smaller studies tended to favor IIV, influenced primarily by two trials conducted among malnourished Indian children (74) and a Hutterite community (77) (Figure 4A).

Age-specific analysis suggested a trend toward better performance of LAIV in younger children, although this difference was not statistically significant (Figure 4B).

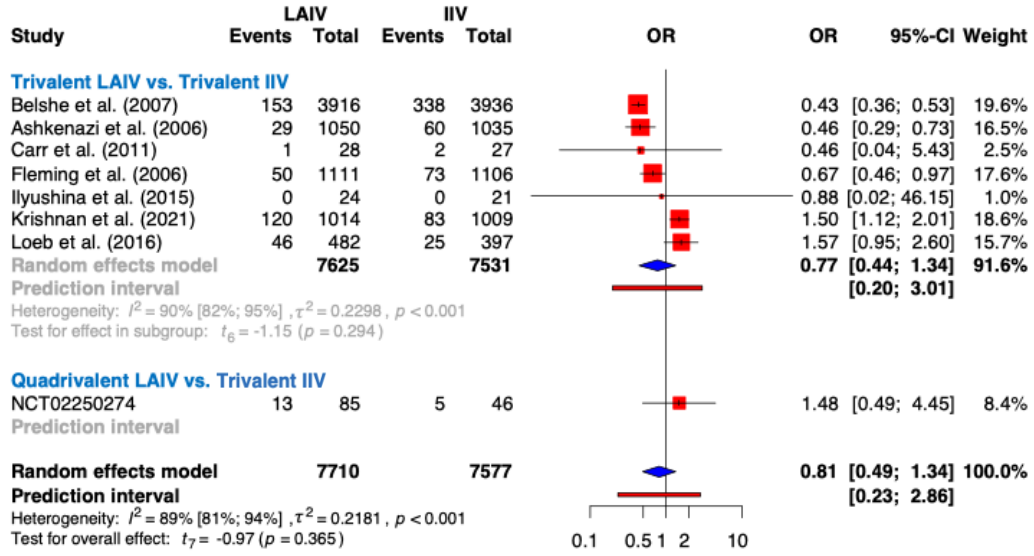


Figure 3. Forest plot representing the OR with 95% CI for confirmed influenza cases, separating trivalent LAIV-IIV comparisons from the single quadrivalent LAIV versus trivalent IIV trial (1)

Squares represent study-specific odds ratios (OR), with the center of the square indicating the point estimate and the horizontal line showing the 95% confidence interval (95% -

CI). The size of the squares is proportional to study weight. Diamonds represent pooled estimates.

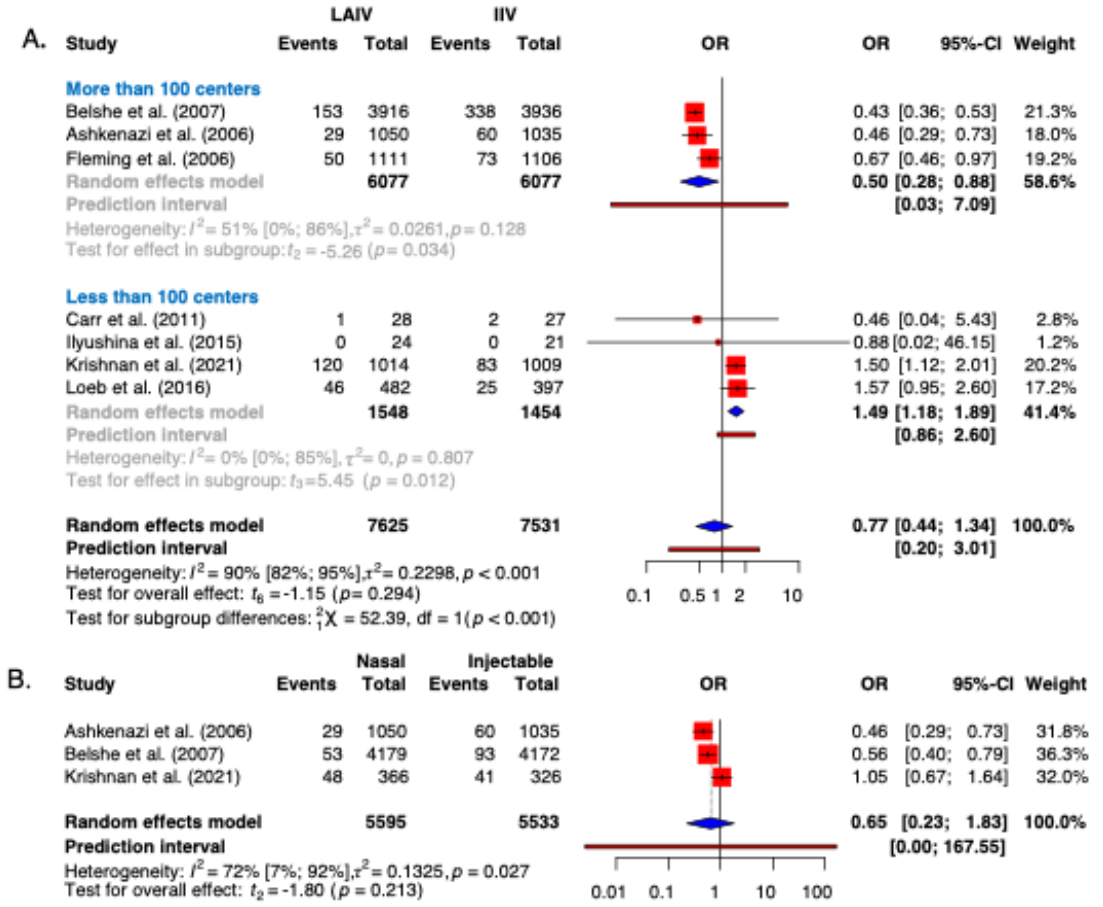


Figure 4. Forest plots representing the OR with 95% CI for confirmed influenza cases (32)

A.) Subgroup analysis comparing large multicenter studies (>100 centers) with smaller studies (<100 centers).

B.) Subgroup analysis of children younger than 6 years of age.

Squares represent study-specific odds ratios (OR), with the center of the square indicating the point estimate and the horizontal line showing the 95% confidence interval (95% - CI). The size of the squares is proportional to study weight. Diamonds represent pooled estimates.

8.1.3. Secondary Outcomes

8.1.3.1. Safety

Safety findings were derived from 19 trials, encompassing data from over 17,000 participants. We could report on a wide range of adverse events. (Table 3).

a) Mortality

No vaccination-related deaths were reported across the 8958 vaccinated participants (Table 3).

b) Serious adverse events (SAEs)

The incidence of SAEs was significantly higher following trivalent LAIV compared with trivalent IIV. However, if we focused on the number of individuals affected by adverse events, not on the overall event frequency, the difference was no longer significant (Table 3). Across the full dataset, only 23 vaccine-related SAEs were reported among 17,092 trivalent vaccine recipients. None by 741 quadrivalent recipients. Odds ratios 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), nor for children younger than nine years (Table 3).

c) ***Hospitalizations***

In total, rates of hospitalizations were low (N = 316, LAIV: 1.29% vs. IIV: 1.34%) (Table 3).

d) Adverse Events (AEs)

When assessed by event frequency, trivalent LAIV was associated with fewer reported adverse events. However, when outcomes were analyzed according to the number of affected individuals, IIV demonstrated significantly lower odds (Table 3).

e) Specific Adverse Events

A total of 21 predefined adverse event categories were analyzed across trivalent trials (Table 3). A statistically significant difference emerged only for nasal symptoms, which were more frequently reported after LAIV (Table 3).

Two trivalent studies reported asthma exacerbations, both yielded non-significant differences (OR = 1.08, 95%CI = 0.90;1.29 and OR = 1.12, 95%CI = 0.78;1.60), although a meta-analysis was not feasible (71,83).

Specific adverse events associated with quadrivalent LAIV were reported infrequently. Only coughing (OR = 0.88, 95%CI=0.44;1.76) (90), significant wheezing (OR=0.62, 95%CI=0.31;1.21 and OR = 1.67, 95%CI=0.02;137.35) (90,91), and asthma exacerbations (OR = 0.70, 95%CI=0.26;1.90) (92) were available for comparison. None demonstrated statistically significant differences; the limited evidence also precluded meta-analytic synthesis.

Table 3. Comparative safety outcomes of trivalent LAIV vs. IIV displayed in sequence of the level of GRADE and effect size (32)

Lower odds for LAIV			**Lower odds for IIV**			
Outcome	**OR (CI 95%)**	**GRADE**	**Outcome**	**OR (CI 95%)**	**GRADE**	
			Nasal symptoms – large, multi-center studies	1.64 (1.33; 2.02)	High	**Significant**
			Nasal symptoms	1.55 (1.30; 1.86)	Moderate	
			Adverse events by the number of affected people	1.26 (1.14;1.40)	Moderate	
			Serious adverse events	1.17 (1.02;1.34)	Moderate	
Coughing	0.95 (0.86;1.05)	High	Significant wheezing	1.16 (0.86; 1.56)	High	**Non-significant**
Diarrhea	0.98 (0.83; 1.16)	High	Sore throat	1.14 (0.99; 1.32)	High	
Related serious adverse events under nine years of age	0.93 (0.53; 1.63)	Moderate	Vomiting	1.09 (0.78; 1.53)	Moderate	
Chills	0.74 (0.26; 2.11)	Low	Serious adverse events by number of affected people	1.11 (0.96;1.28)	Low	
Having a temperature higher than 38,5C	0.78 (0.37; 1.66)	Low	Decreased activity	1.02 (0.59; 1.76)	Low	
Headache	0.90 (0.62;1.31)	Low	Otitis media	1.48 (0.45; 4.89)	Very low	
Adverse events by the number of reported events	0.51 (0.05;5.09)	Very low	Upper respiratory tract infection	1.64 (0.27; 10.05)	Very low	
Muscle- or body ache	0.56 (0.24; 1.32)	Very low	At least subfebrility under six years of age	1.32 (0.46; 3.75)	Very low	
Hospitalization	0.58 (0.04;7.86)	Very low	Skin reactions	1.27 (0.14;11.65)	Very low	
Adverse events	0.81 (0.36;1.83)	Very low	Nasal symptoms – smaller studies	1.24 (0.89; 1.71)	Very low	
Fever	0.85 (0.50;1.43)	Very low	Nasopharyngitis	1.22 (0.53; 2.79)	Very low	
At least subfebrility above six years of age	0.91 (0.58; 1.43)	Very low	Irritability	1.08 (0.78; 1.49)	Very low	
At least subfebrility	0.93 (0.54; 1.61)	Very low	Related serious adverse events	1.07 (0.70;1.62)	Very low	
Decreased appetite	0.94 (0.66; 1.35)	Very low	Ear or eye reactions	1.06 (0.47; 2.40)	Very low	
Wheezing	0.98 (0.73; 1.33)	Very low				

OR: odds ratio; CI:confidence interval; LAIV: live-attenuated influenza vaccine; IIV: inactivated influenza vaccine; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

8.1.3.2. Cost-effectiveness

All three analyses, which were based on previous RCTs, reached a uniform conclusion, indicating that LAIV is the more cost-effective option (Table 2). However, we were unable to perform a quantitative synthesis due to the lack of reporting confidence intervals in two out of three studies. According to the trials, LAIV's higher protection rate resulted in fewer healthcare visits and reduced caregiver productivity loss. These advantages outweighed the higher unit cost of LAIV across all modeled scenarios (78,80,82).

No cost-effectiveness evaluations were identified for quadrivalent vaccine comparisons.

8.1.4. Risk of Bias Assessment

Most efficacy trials were judged to have a low risk of bias. In contrast, the safety dataset demonstrated more variability in methodological rigor. Six of the nineteen studies were judged to have an overall high risk of bias, most commonly due to incomplete outcome reporting or unclear ascertainment of adverse events.

Visual inspection of funnel plots did not suggest substantial asymmetry (Figure 4), and Egger's test for the "at least subfebrility" outcome did not indicate evidence of small-study effects ($t = -0.13$, $df = 8$, $p = 0.90$).

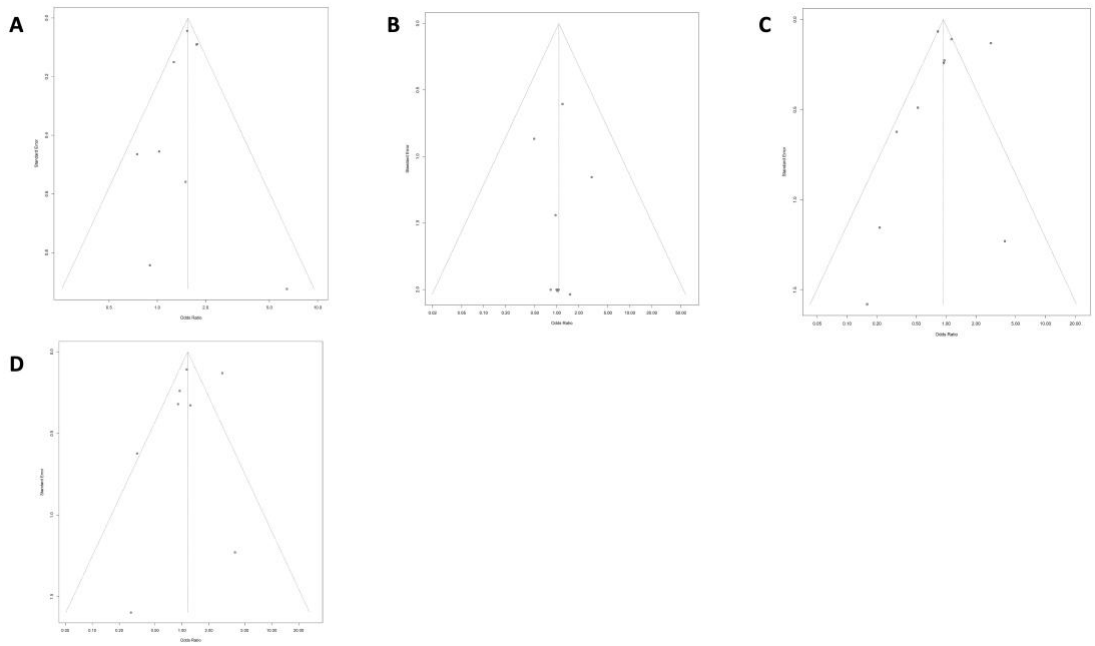


Figure 4. Funnel plots assessing potential publication bias for safety outcomes:
(A) nasal symptoms; (B) vaccine-related serious adverse events; (C) at least subfebrility; and (D) at least subfebrility, subgroup analysis by age (<6 years vs ≥6 years) (32)

Each dot represents an individual study. The vertical line indicates the pooled effect estimate, and diagonal lines represent the 95% pseudo–confidence limits.

8.1.5. Quality of Evidence

Using the GRADE framework, the certainty of evidence supporting greater efficacy of trivalent LAIV, particularly when informed by large, multi-center randomized controlled trials, was rated as high. In contrast, safety outcomes showed substantially lower certainty. Among the 34 trivalent safety comparisons, over half (24/34) were graded as low or very low (Table 3). All safety outcomes related to quadrivalent formulations were graded as very low certainty, reflecting sparse data and wide confidence intervals (32).

8.1.6. Quality of Evidence

Using the GRADE framework, the certainty of evidence supporting greater efficacy of trivalent LAIV, particularly when informed by large, multi-center randomized controlled trials, was rated as high. In contrast, safety outcomes showed substantially lower certainty. Among the 34 trivalent safety comparisons, over half (24/34) were graded as low or very low (Table 3). All safety outcomes related to quadrivalent formulations were graded as very low certainty, reflecting sparse data and wide confidence intervals.

8.2. Study II – Long COVID

8.2.1. Study Population

A total of 89 children with confirmed prior SARS-CoV-2 infection were included. The cohort had a mean age of 11.4 ± 3.8 years, ranging from preschool age to late adolescence, with a notable female predominance (63%) (Table 4). Most experienced a mild or asymptomatic acute COVID-19 (94%). None had received the SARS-CoV-2 vaccination before their first visit.

Table 4. Patient characteristics (40)

Characteristics	Overall	(%)	Male	(%)	Female	(%)	P Male vs. Female	g/r [95% CI]
Ethnicity,n								
Caucasian	89	*(100)*	33	*(37)*	56	*(63)*		
Mean age, years (SD)	11.4	(3.8)	10.1	(4.2)	12.3	(3.2)	**0.015**	0.60 [0.16;1.03]
Age groups, n								
0-5 years	6	*(6)*	6	*(18)*	0	*(0)*		
6-11 years	36	*(40)*	13	*(40)*	23	*(41)*		
12-18 years	47	*(56)*	14	*(46)*	33	*(59)*		
Long COVID symptoms per children, n (SD)[a]	12	(8)	10	(8)	13	*(7)*	0.11	0.34 [-0.08;0.79]
Mean symptom duration, weeks (SD)	18	(8)	15	(7)	20	(8)	**0.003**	0.66 [0.21;1.10]
Long COVID complaints related to an organ system, n								
General	77	*(87)*	30	*(91)*	47	*(84)*	0.52	0.1 [-0.11;0.31]
Neurologic	74	*(83)*	26	*(79)*	48	*(86)*	0.40	0.09 [-0.12;0.30]
Mental	64	*(72)*	18	*(55)*	46	*(82)*	**0.007**	0.31 [0.09;0.52]
Cardiovascular	55	*(62)*	20	*(61)*	35	*(63)*	0.86	0.02 [-0.13;0.23]
Gastrointestinal	53	*(60)*	18	*(55)*	35	*(63)*	0.51	0.08 [-0.13;0.29]
ENT-O	49	*(55)*	13	*(39)*	36	*(64)*	**0.028**	0.25 [0.03;0.46]
Musculoskeletal	40	*(45)*	13	*(39)*	27	*(48)*	0.51	0.09 [-0.12;0.29]
Pulmonary	30	*(34)*	10	*(30)*	20	*(36)*	0.65	0.06 [-0.15;0.26]
Dermatologic	23	*(26)*	12	*(36)*	11	*(20)*	0.13	0.19 [-0.02;0.40]
Reproductive[b]	11	*(12)*	0	*(0)*	11	*(20)*		
Occurrence of Long COVID symptoms after acute COVID-19 disease, n								
continuously present	58	*(65)*	25	*(76)*	33	*(59)*		
1-2 weeks later	9	*(10)*	3	*(9)*	6	*(11)*		
3-4 weeks later	13	*(15)*	3	*(9)*	10	*(18)*		
>1 month later	9	(10)	2	(6)	7	(12)		
Quality of long COVID complaints, n								
Completely new complaint	73	*(82)*	26	*(79)*	47	*(84)*		
Change in the intensity/ quality	10	*(11)*	3	*(9)*	7	*(12)*		
Not clear	6	*(7)*	4	*(12)*	2	*(4)*		

CI: confidence interval, g/r: group ratio; ENT-O = ear-nose-throat & ophthalmology, n: number of people, p: p- value, SD: standard deviation

[a] The number of reported symptoms could not exceed 50.

[b] Only two questions addressed the complaints in the reproductive system: if they had erectile dysfunction, and if they had dysmenorrhea, and only dysmenorrhea occurred. Therefore, the comparison of the gender distribution in this category is biased.

8.2.2. Primary Outcomes

8.2.2.1. Symptom scale

Symptom duration at the time of first clinical evaluation ranged from 5 weeks to 37 weeks (9.3 months), with an average of 4.5 months. More than half of the children (65%) reported that at least one symptom had been continuously present since their acute illness, while an additional group developed symptoms weeks after recovery from the acute infection, including 10% whose complaints emerged more than one month later (Table 4). The average number of reported persistent symptoms was 12 per child (range 1-33), involving a mean of five organ systems (Table 4).

Across the registry, persistent fatigue was the most prevalent symptom, reported by 70% of participants. Other high-frequency complaints included loss of interest or pleasure, headaches, concentration difficulties, dizziness, sleep disturbances, and post-exertional

malaise. Chemosensory disorders, including alterations in smell or taste, were reported in 28% of cases (Figure 5).

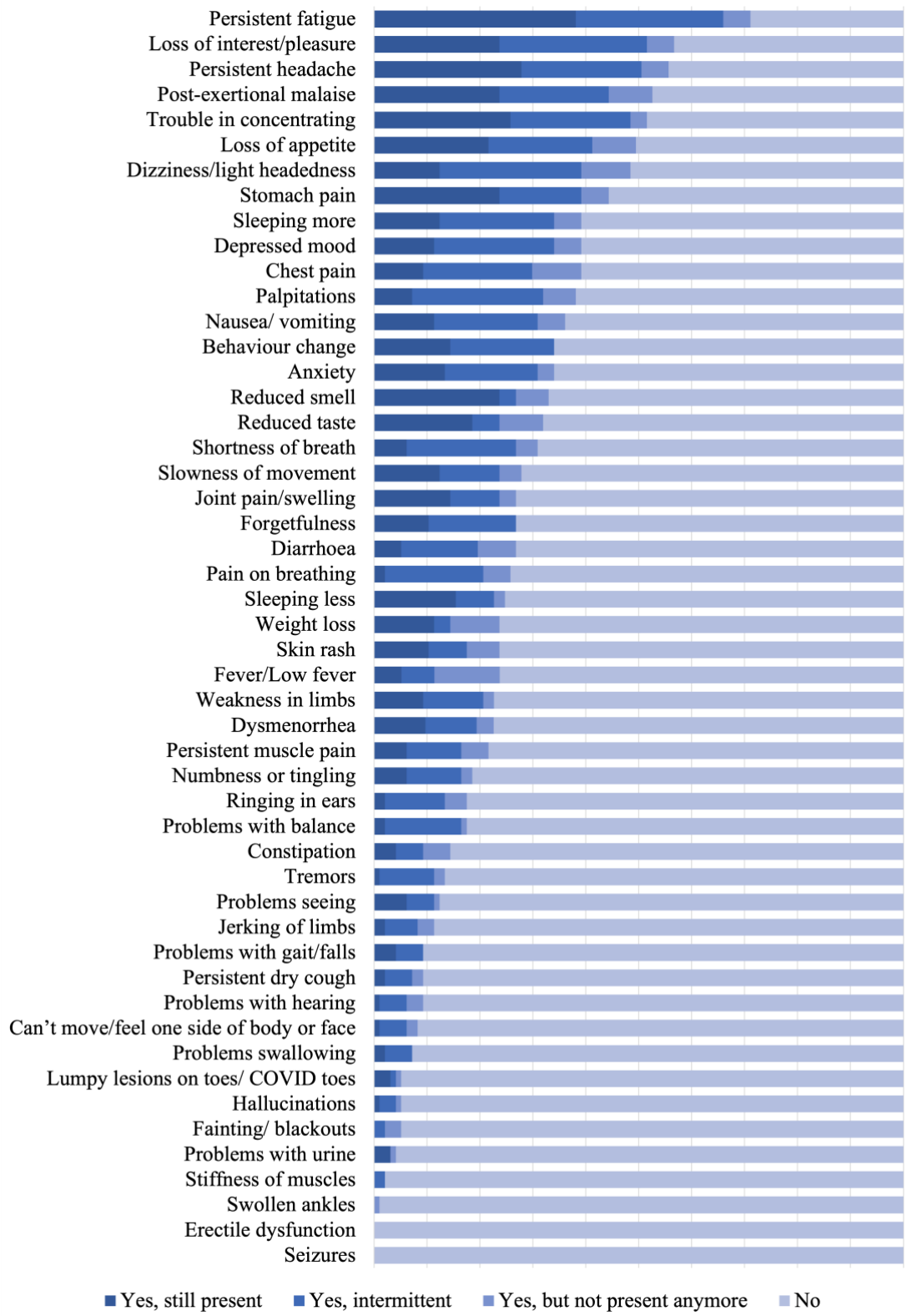


Figure 5. Distribution of symptom severity among children with long COVID (40)

Symptom severity was assessed using a standardized scale, with stacked bars indicating the proportion of children reporting increasing levels of severity for each symptom.

8.2.2.1. Corresponding medical findings

We conducted more than 300 medical examinations to investigate the causes of the symptoms (Table 5). At least mild, objective clinical findings were documented in approximately one-quarter of cases (Table 5). Organ-specific diagnostic evaluations revealed that 18% of symptoms corresponded to objective medical findings within their respective symptom category (Table 5). Positive findings connected to complaints were most frequently identified in the respiratory category (38%) (Table 5).

Table 5. Frequency of investigations by organ-specific complaint, including rates of positive and symptom-concordant findings (40)

Number of patients with at least one group specific COMPLAINT	Examination	Positive findings/ Performed examinations (positive findings %)	Number of patients with at least one positive finding in the subgroup/number of patients with at least one group specific complaint, n (matching complaints %)
GENERAL (n=77)		**21/85 (25%)**	**21/77 (27%)**
	Neck US	7/9 (78%)	
	Thyroid screening	11/85 (12%)	
	6mWT[a]	10/29 (34%)	
NEUROLOGIC (n=74)		**5/44 (11%)**	**5/74 (7%)**
	Neurological examination	5/43 (12%)	
	Head MRI[b]	2/11 (18%)	
	Spinal MRI	0/1 (0%)	
	CSF[c]	2/2 (100%)	
	EEG	0/7 (0%)	
MENTAL HEALTH (n=64)		**15/24 (63%)**	**15/64 (23%)**
	Mental specialist consultation	15/24 (63%)	
CARDIOVASCULAR (n=55)		**8/44 (18%)**	**8/55 (15%)**
	Echocardiography	5/39 (13%)	
	Cardiac MRI	0/1 (0%)	
	ECG	4/44 (9%)	
	Holter ECG	0/2 (0%)	
GASTROINTESTINAL (n=53)		**8/37 (22%)**	**8/53 (15%)**
	Abdominal US	6/35 (17%)	
	Celiac disease screening	0/11 (0%)	
	Stool occult blood test	0/12 (0%)	
	Stool culture	0/10 (0%)	
	H_2 breath test	2/2 (100%)	

Table 5. Frequency of investigations by organ-specific complaint, including rates of positive and symptom-concordant findings (continued) (40)

Number of patients with at least one group specific COMPLAINT	Examination	Positive findings/ Performed examinations (positive findings %)	Number of patients with at least one positive finding in the subgroup/number of patients with at least one group specific complaint, n (matching complaints %)
EAR-NOSE-THROAT & OPHTHALMOLOGY (n= 49)		**8/41 (20%)**	**8/49 (16%)**
	ENT specialist consultation	3/16 (19%)	
	Ophthalmology specialist	7/32 (22%)	
MUSCULOSKELETAL (n=45)		**2/5 (40%)**	**2/40 (5%)**
	Knee US	2/3 (67%)	
	Other imaging examinations[d]	1/2 (50%)	
PULMONARY (n=30)		**11/40 (28%)**	**11/30 (37%)**
	Chest CT	0/3 (0%)	
	Pulmonary US	0/1 (0%)	
	Chest X-Ray	4/33 (12%)	
	Lung function test	11/24 (46%)	
DERMATOLOGIC (n=23)		**5/8 (63%)**	**5/25 (20%)**
	Dermatology specialist consultation	5/8 (63%)	5/23 (22%)
TOTAL		**83/328 (25%)**	**83/465 (18%)**

6mWT: 6-minute walking test, CSF: cerebrospinal fluid, CT: computed tomography, ECG: electrocardiogram, EEG: electroencephalogram, MRI: magnetic resonance imaging, US: ultrasound
[a]Subject had to stop during the 6 minutes, or had a drop in SpO2 <95%, or their heart rate elevated to 1.5x of their resting heart rate.
[b]Positive MRIs were considered potentially normal variants by agreement between a radiologist and a pediatric neurology specialist.
[c]Positive CSF samples showed only marginally elevated protein levels and were considered to be of low clinical importance by a pediatric neurology specialist. [d]Hip US, shoulder US, sternocostal MRI [e]Chest X-Rays were performed because of pulmonary and/or cardiological reasons.

8.2.3. Secondary Outcomes

8.2.3.1. Physical examination and laboratory testing

During physical examination, 51% of children had at least one detectable finding. Although most of them were mild, such as abdominal tenderness. Several clinically relevant signs were documented, including exercise intolerance, abnormal neurologic findings, cutaneous manifestations, and cardiopulmonary abnormalities.

Most laboratory deviations were mild or of uncertain clinical significance.

The positivity rate of performed imaging examinations was 28%.

8.2.3.2. Autoimmune thyroiditis

Based on elevated thyroid autoantibodies, we found ten children with thyroid autoimmunity (12%) (Table 5). Four children also had elevated TSH levels.

Based on confirmatory ultrasound, the rate of newly diagnosed autoimmune thyroiditis was 7%.

8.2.3.3. Cardio-pulmonary assessments

Pulmonary examinations requested by our team yielded a relatively high diagnostic rate, with 46% of lung function tests showing abnormalities, almost all of which were attributed to obstructive pulmonary disease (Table 5).

Cardiology-directed examinations identified abnormalities in 15% of evaluated children, revealing isolated cases of suspected myocarditis, post-viral tachycardias, and a newly recognized long QT syndrome (Table 5).

Thirty-four percent of children completing a 6-minute walk test exhibited clinically significant findings (oxygen desaturation, need to stop, or substantial tachycardia).

8.2.3.4. Neurologic evaluations

Those who underwent neurology-related examinations were found to have non-physiologic findings in 7% with conditions such as trigeminal cephalalgia with polyneuropathy (Table 5).

8.2.3.5. Gastrointestinal evaluations

Among children with gastrointestinal complaints, who were referred for an abdominal ultrasound, celiac-, stool-, or breath testing, positive findings were detected in 15%, including lactose intolerance, dysbiosis, and hepatic steatosis (Table 5).

8.2.3.6. Dermatologic consultations

Dermatology specialist assessments led to positive findings in 63% of evaluated cases, including one child who had previously developed Schönlein-Henoch purpura, possibly associated with COVID-19 (Table 5).

8.2.3.7. Mental health

Mental health symptoms were common (reported by 72%), and formal evaluation resulted in new preliminary diagnoses in nearly one quarter of those assessed, most frequently with anxiety and depression (Figure 5,8, Table 5).

8.2.3.8. Quality of Life (Functioning)

Among the 67 children who completed at least half of the questionnaire, mean functioning scores were mostly consistent with mild functional limitations (*Mean* = 27.1, *SD* = 22.8, min-max: 0-90.9) (Figure 6A). Comparison with pre–COVID–19 functioning indicated a predominantly worsened functional status (*Mean* = 70.4, *SD* = 16.3, min-max: 45.8-100)

(Figure 6B). Notably, 26% of participants exhibited both moderate-to-severe functional impairment (QoL-F ≥ 50) and a clear decline relative to their pre-infection baseline (Figure 6C). The domains most frequently affected were emotional well-being, concentration, physical endurance (including prolonged walking or standing), and participation in school-related daily activities (Figure 6). The ability to perform self-care was evaluated using a separate item. Of the 73 children who responded, 21 (29%) reported impaired functioning, whereas 52 (71%) reported no change.

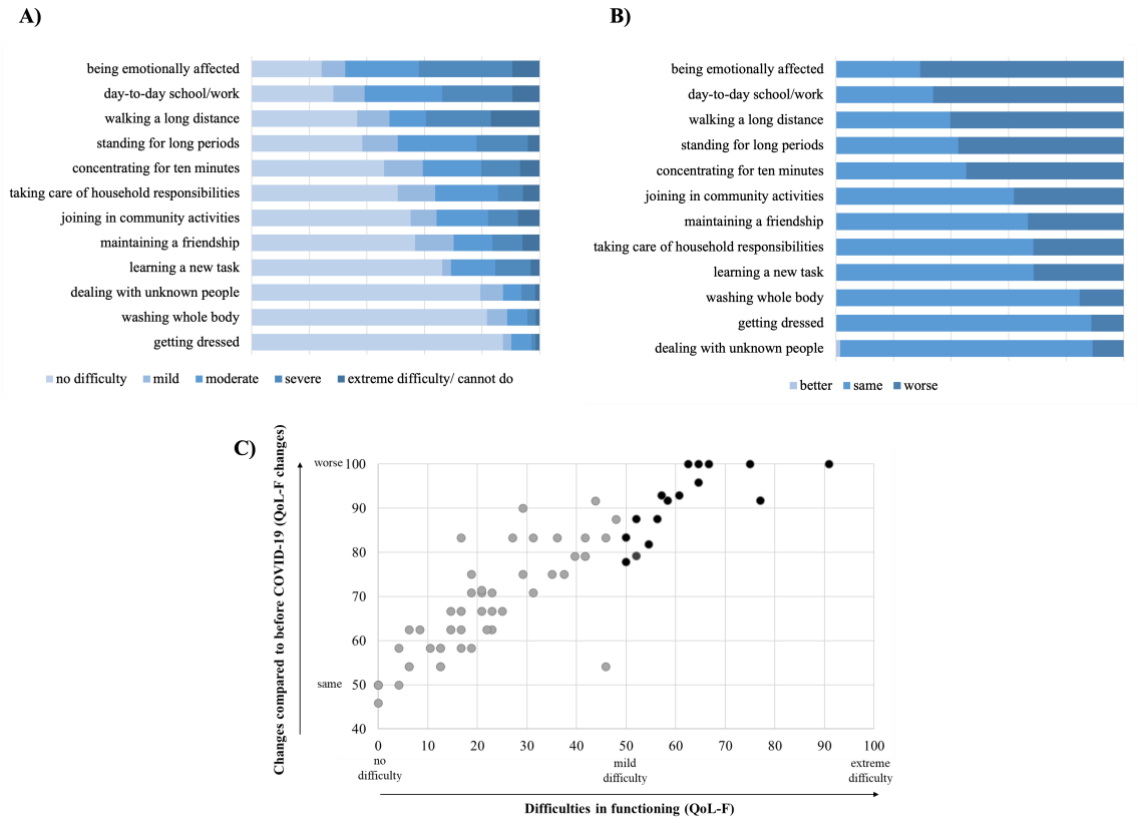


Figure 6. Functional impairment among children with long COVID (40)

(A) Distribution of difficulties across 12 domains of daily functioning. Responses are shown on a five-level ordinal scale ranging from no difficulty to extreme difficulty or inability to perform the activity.
(B) Self-reported change in the same domains compared with the pre-COVID period, categorized as better, unchanged, or worse.
(C) Relationship between current functional difficulties (QoL-F score) and perceived change since COVID-19 (QoL-F change score).

8.2.4. Subgroup and Sensitivity Analyses

8.2.4.1. Sex

Females were older than males; they reported more symptoms per capita, more mental health and ear-nose-throat or eye-related complaints and had a significantly longer mean symptom duration (20 vs. 15 weeks) (Table 4).

8.2.4.2. Age

Older children had experienced symptoms for a longer duration at the time of our visit ($r = 0.58$, 95%CI: 0.42;0.7, df:87, $p < 0.001$).

8.2.4.3. Symptom-onset timing

While the majority developed symptoms during their acute illness, a meaningful minority (approximately 25%) developed symptoms weeks later, and 10% only after one month.

8.2.5. Additional Findings or Exploratory Analyses

8.2.5.1. Symptom mapping

Symptom co-occurrence mapping revealed that general, neurological, mental health, gastrointestinal, and cardiopulmonary complaints frequently clustered (Figure 7).

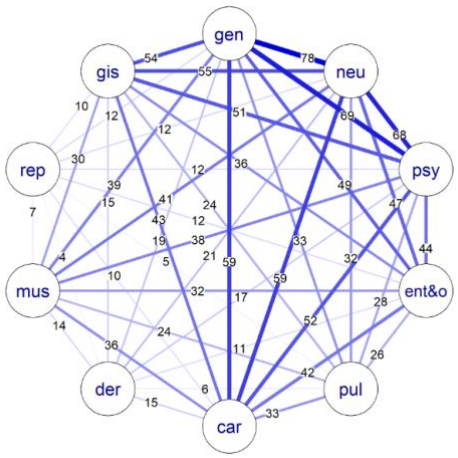


Figure 7. Symptom co-occurrence network in children with long COVID (40)

Nodes represent symptom categories (general, neurologic, mental health, gastrointestinal, cardiopulmonary, musculoskeletal, dermatologic, respiratory, and ear–nose–throat/ophthalmologic). Edges indicate co-occurrence between symptom categories, with line thickness proportional to the frequency of co-occurrence and numerical labels denoting the number of children reporting both symptom categories.

8.2.5.2. Acute vs. long

As in acute COVID-19, general and neurological symptoms predominated at the lingering phase; however, mental and cardiologic complaints were more frequently reported in long COVID syndrome than during the acute phase (Figure 8).

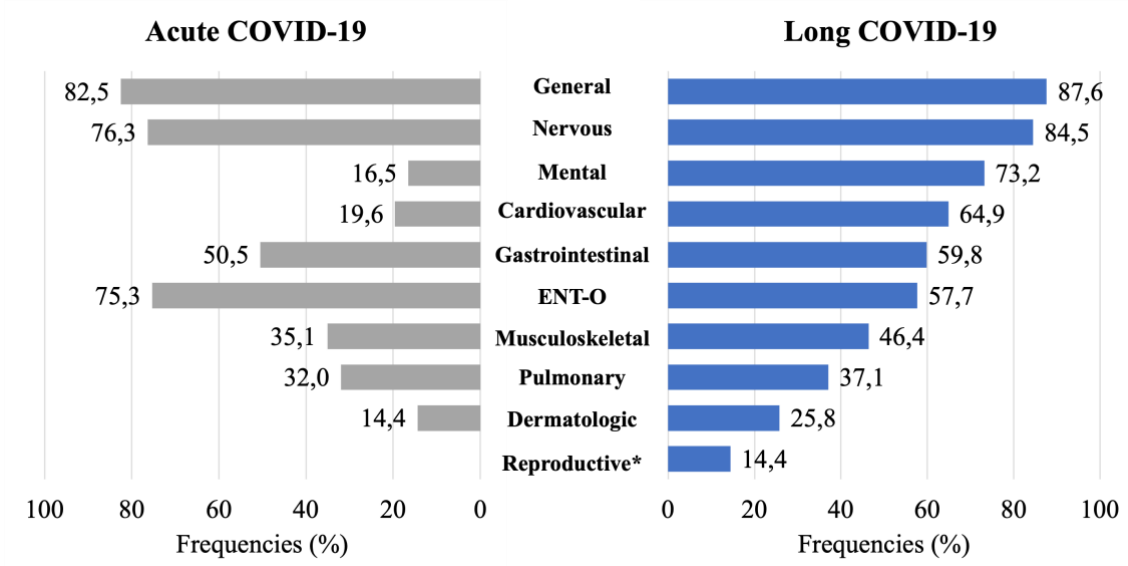


Figure 8. Comparison of symptom category frequencies during acute COVID-19 and long COVID within the same cohort of children (40)

Frequencies indicate the percentage of children reporting at least one symptom within each organ-system category at each disease phase.

ENT-O: ear–nose–throat/ophthalmologic

8.2.5.3. Diagnostic imaging

Low-dose computed tomography scans performed early in the clinic's operation revealed no structural pulmonary abnormalities, leading to a shift toward non-radiation investigations.

9. DISCUSSION

9.1. Summary of Findings, International Comparisons

Through two complementary studies, a large-scale systematic review and meta-analysis of pediatric influenza vaccines and a population-based registry analysis of children with long COVID syndrome, this work sought to advance the understanding of pediatric viral infections by addressing preventive strategies and post-infectious long-term outcomes. Collectively, our findings highlight two central challenges in pediatric viral infection control: optimizing effective preventive interventions and strengthening health care systems to address prolonged, multisystem morbidity following acute viral infections.

9.1.1. Prevention: Influenza Vaccination

Our systematic review and meta-analysis of head-to-head randomized controlled trials, comprising data on more than 15,000 children, demonstrated that LAIV and IIV show similar overall efficacy in preventing laboratory-confirmed influenza in children. However, when data were restricted to large, multicenter trials, LAIV showed superiority over IIV, suggesting enhanced real-world performance in more diverse, representative populations. Similarly, a recent network meta-analysis of observational studies indicated comparable moderate overall effectiveness for both vaccine types with varying strain-specific performance over seasons (93,94).

The heterogeneity observed across smaller trials is concordant with global variability in the impact of vaccination, as effectiveness may differ by influenza season based on the circulating virus subtype and the vaccine's strain-specific effectiveness (93). Factors, such as host-specific variables, including nutritional status, pre-existing immunity, immunosuppressive conditions, and sociocultural determinants, have also been shown to modulate immunogenicity and clinical effectiveness (95–98).

The safety profile across more than 17,000 children was reassuring, as no vaccine-related deaths and only 23 vaccine-related serious adverse events were observed, with no significant difference between LAIV and IIV. This aligns with global pharmacovigilance data, which confirms that vaccines are among the safest interventions in pediatric care (99–101). Economic evaluations consistently favored LAIV due to reductions in influenza incidence, healthcare utilization, and parental productivity loss. According to a systematic review, cost-effectiveness is primarily driven by vaccine effectiveness,

coverage rates, herd immunity, and local economic parameters, emphasizing that both influenza vaccines are cost-effective, and advising tailored decision-making (102).

9.1.2. Long COVID

Our registry analysis of 89 Hungarian children with long COVID revealed substantial and persistent multisystem morbidity following SARS-CoV-2 infection at our single-center, descriptive early pandemic study. Based on our study, we were unable to determine prevalence estimates. International data remain highly variable, ranging from <1% to >40% across studies, reflecting heterogeneity in case definitions, study populations, symptom assessment methods, reliance on self-reported data, and the availability and selection of control groups (103).

Despite predominantly mild acute disease, affected children experienced a high burden of concurrent symptoms involving general, neurological, cardiopulmonary, gastrointestinal, and mental health domains, with measurable impact on everyday functioning in our cohort. In contrast, a recent meta-analysis comparing infected children with controls identified significantly increased risk only for persistent dyspnea, anosmia/ageusia, and fever. In our cohort, a subset of patients reported extensive multisystem complaints that persisted for a median of 4.5 months at the time of first evaluation, a point when the expected duration and prognosis of long COVID in children were still poorly defined. More recent international data suggest that the long-term prognosis is favorable for most children, with symptom resolution occurring within approximately six months (103,104).

Our cohort showed an approximately 2:1 female-to-male ratio, with females reporting a higher symptom burden, consistent with studies identifying female sex, older age, and comorbidities as risk factors for persistent symptoms (105). The predominance of school-aged children mirrors other international reports (106). We also hypothesized that symptom profiles differ by age, particularly between younger and older children, a notion subsequently supported by findings from the large-scale “Researching COVID to Enhance Recovery” (RECOVER)– Pediatrics cohort (107,108).

We observed a pronounced mismatch between symptom burden and objective clinical findings, consistent with international reports suggesting that distinguishing post-COVID–related symptoms from pandemic-associated psychosocial effects is challenging (40,109). However, to our knowledge, no similar clinically oriented, but larger-scale

controlled pediatric clinical study with laboratory-confirmed COVID-19 has been published to date.

Nevertheless, in a minority of cases, clinically significant conditions with potential therapeutic implications, such as autoimmune thyroiditis or obstructive respiratory disorders, were identified in our cohort. At the same time, certain diagnoses identified during evaluation, such as long QT syndrome, are not typically considered part of the pediatric long COVID spectrum (110). These findings likely reflect coincidental or previously unrecognized conditions rather than SARS-CoV-2–associated sequelae, highlighting the importance of comprehensive diagnostic assessment.

Following our initial observations, substantial further research, including work by our own research group, has explored potential links between SARS-CoV-2 infection and autoimmune conditions such as autoimmune thyroiditis, type 1 diabetes, and celiac disease (111–113). Although we could not demonstrate a causal association between COVID-19 and thyroid autoimmunity, in our subsequent study, we reported a prevalence of thyroid autoimmunity of 6.6% and autoimmune thyroiditis of 4.0% among 458 individuals, with long-term alterations present in the majority (111). Moreover, one of our early observational reports described higher incidence rates of type 1 diabetes after the onset of the pandemic, which were subsequently corroborated by a meta-analysis (112,114). Our latest findings indicate a long-term rise in thyroid autoimmunity among children with type 1 diabetes, but independent of SARS-CoV-2 infection (115). Although universal celiac screening, which we initiated in July 2021, revealed a higher-than-expected prevalence, current evidence does not support SARS-CoV-2 infection as a trigger for celiac disease in children, indicating that these findings are likely incidental or related to increased diagnostic intensity (113,116).

Current evidence suggests that long COVID is a multifactorial condition with overlapping pathogenic mechanisms, including viral persistence, immune dysregulation with or without latent virus reactivation, microbiome alterations, autoimmunity, endothelial and microvascular dysfunction, neuroautonomic disturbances, and mitochondrial impairment (117,118). In parallel, our working group conducted a detailed clinical and immunological study, demonstrating a higher symptom burden and significantly reduced functioning in children with long COVID compared to convalescent controls. Our working group also identified impaired neutrophil functions that correlated with symptom

severity, supporting a potential role for innate immune dysfunction in the pathophysiology or susceptibility to pediatric long COVID (119).

9.1.3. Integrated Perspective

Taken together, these studies underscore that effective prevention of viral infections in childhood is critical not only for reducing acute morbidity but also for potentially limiting long-term sequelae. However, evidence regarding the role of vaccination in preventing long COVID remains heterogeneous, with current data providing only a low level of evidence for a protective effect (120).

9.2. Strengths

Together, these studies offer a uniquely integrated perspective on pediatric viral infections. Our work addresses critical gaps in pediatric infectious disease research, employs robust and transparent methodologies, and provides results directly relevant to clinical care and public health policy.

Our systematic review included only randomized controlled trials, the highest level of evidence for evaluating the causality of interventions and their outcomes. This design minimized confounding and selection bias, allowing for a rigorous comparison between LAIV and IIV. The analysis incorporated large multicenter trials from diverse geographic regions, which enhances the generalizability of the findings and reflects real-world epidemiological conditions more accurately than single-center studies. Adherence to PRISMA guidelines, PROSPERO, the use of RoB2 and GRADE frameworks, and the incorporation of sensitivity analyses ensured transparency and methodological rigor. Finally, we evaluated not only efficacy but also safety and cost-effectiveness, enabling a multidimensional assessment of both vaccines within a unified framework. This comprehensive approach allows for more meaningful policy translation than efficacy estimates alone.

The long COVID study's primary strength lies also in its systematic approach and the in-person, clinician-led assessment using a standardized protocol. Unlike many international long COVID cohorts relying solely on parent-or self-reported symptoms, this study incorporated detailed history-taking, physical examination, laboratory testing, imaging, and targeted specialist evaluations. Conducting the study early in the pandemic reduced bias related to prior vaccination and reinfection. Symptoms were precisely categorized

into organ-system groups, and their frequency, intensity, duration, and co-occurrence patterns were systematically documented. More than 300 symptom-driven diagnostic pathways were evaluated (Table 5). This level of structured clinical assessment is rarely available in pediatric long COVID studies, positioning the dataset as one of the more detailed pediatric cohorts published to date. The inclusion of quality-of-life assessments, evaluated using standardized tools and the comparison to pre-COVID status, adds further value.

9.3. Limitations

9.3.1. Influenza Vaccination

Heterogeneity across trials related to population characteristics, circulating strains, antigenic match, and study period might limit the precision of pooled estimates. Direct quadrivalent-to-quadrivalent efficacy comparisons were unavailable; quadrivalent-to-quadrivalent safety data and quadrivalent-to-trivalent efficacy data were sparse, precluding definitive conclusions. Comparing only active-controlled studies substantially reduced the number of included trials, reflecting a shift toward test-negative designs that are less costly and more ethically feasible. Furthermore, the interpretation of active-controlled trials is challenging due to the absence of placebo comparators, underscoring the importance of concomitant placebo-controlled efficacy data for contextualizing comparative effectiveness results (121). The data did not allow robust age-stratified safety or efficacy analyses. Variation in reporting of adverse events and economic outcomes also constrained certain analyses.

9.3.2. Long COVID

We captured children seeking care for persistent symptoms, who may therefore be more likely to represent cases of more severe long COVID. Absence of a SARS-CoV-2 negative control group restricts causal inference. The limitations of current diagnostic tools may lead to the omission of subtle abnormalities, resulting in a mismatch between symptoms and clinical findings. The cross-sectional nature of the first visit data restricts insight into longitudinal recovery trajectories. Families' recall of pre-pandemic health status may have introduced reporting bias, while symptom duration estimates and study participation may also have been influenced by the timing of clinic opening, limited capacity, and reliance on primarily online appointment registration.

10. 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 sequelae.

10.1. 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-effectiveness benefits.

10.2. 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. Potential increases in autoimmune disease prevalence underscore the need for ongoing surveillance and focused research.

11. IMPLICATIONS FOR PRACTICE

11.1. Study I. - Influenza vaccination

Our meta-analysis supports the consideration of LAIV as a central component of pediatric influenza prevention policies, given its comparable effectiveness and safety relative to IIV. The needle-free administration of LAIV represents an important implementation advantage, with the potential to improve acceptability among children and caregivers and to facilitate delivery in non-traditional settings (22,23,122,123). Regulatory approval for self- or caregiver administration in the United States further illustrates its potential role in expanding access (124).

11.2. Study II. – Long COVID

Currently, no validated biomarker exists for pediatric long COVID, and until its long-term pathological sequelae are better understood, diagnosis remains one of exclusion. This approach often necessitates extensive investigations, placing considerable physical and psychological burden on affected children and their families (40,103).

Moreover, no disease-modifying causal therapy has yet been established for post-acute infection syndromes, including long COVID. Consequently, current management still relies on individualized, holistic care, emphasizing patient and family education, structured self-management strategies, and multimodal, multidisciplinary non-pharmacological interventions, with pharmacological treatment guided by symptom-specific recommendations (103,125).

12. IMPLICATIONS FOR RESEARCH

12.1. Study I. – Influenza vaccination

Until a "universal" influenza vaccination becomes available, there is a need for contemporary, adequately powered head-to-head trials comparing LAIV and IIV across multiple seasons and diverse populations. Because vaccine performance is strongly influenced by circulating strains, population characteristics, and contextual factors, future study designs must prospectively account for these variables with a particular emphasis on age and children from subtropical and tropical regions (95–98). Standardized reporting of outcomes, including efficacy, safety, and cost-effectiveness, would substantially improve comparability across trials. Evidence regarding the safety of LAIV in children under two years of age and in other high-risk groups, as children with asthma or wheezing, remains limited, highlighting the need for further pediatric safety studies (99,126). These areas are crucial for optimizing vaccine policy in a rapidly evolving viral landscape (52).

12.2. Study II. – Long COVID

Our findings highlight the need for continued investigation into the biological mechanisms underlying persistent symptoms in pediatric long COVID. The identification of reliable biomarkers may enhance diagnostic accuracy, risk stratification, and the development of targeted therapeutic approaches (41). Future research should address the marked heterogeneity of symptom profiles through detailed phenotyping and determine which clinical features or symptom constellations justify more extensive evaluation. In addition, well-designed pediatric interventional studies and long-term follow-up cohorts are required to inform evidence-based management strategies and clarify disease trajectories.

13. IMPLICATIONS FOR POLICY MAKERS

13.1. Study I. - Influenza vaccination

Policy initiatives that address structural, financial, and behavioral barriers to vaccination have the potential to substantially increase pediatric vaccine uptake (52). Policymakers should therefore consider integrating LAIV as a key component of national pediatric influenza programs, particularly in settings with established immunization infrastructures, such as institute-based programs (23,32,127). High vaccination coverage among children is particularly impactful, as it reduces community transmission and provides indirect protection to high-risk populations (52). However, significant policy gaps persist, as LAIV remains unavailable or unfunded in many countries due to regulatory, reimbursement, and procurement constraints (24–26,128). In an era marked by global demographic change, vaccine hesitancy, and persistent influenza-associated morbidity, there is a need for context-specific vaccination policies that account for local epidemiology, seasonality, and health system capacity, rather than reliance on a uniform global approach (29,129).

13.2. Study II. – Long COVID

The findings of this study highlight the need for coordinated, internationally harmonized pediatric long COVID care pathways and emphasize that health systems must recognize long COVID as a condition that can affect children even after mild acute infection. This is why we contributed to the work of the International Post-COVID-Condition in Children Collaboration (IP4C) (40,130). Policymakers should support the development of standardized clinical assessment frameworks to guide healthcare providers in managing children with persistent, fluctuating, and multisystem symptoms, especially given the limited diagnostic yield of routine investigations. Because many affected children experience reduced functional capacity, emotional symptoms, and school difficulties, health policy must prioritize access to multidisciplinary care, integrating pediatrics, mental health, rehabilitation, and educational support services. Ensuring that such care is available and equitable is essential for mitigating long-term impacts on children's daily functioning and well-being.

Policymakers should therefore promote the development and adoption of standardized criteria, encourage the creation of pediatric long COVID registries, and support research infrastructure that enables consistent data collection and international comparability.

We have the opportunity to investigate a post-viral syndrome in large cohorts, representing an unprecedented situation in the history of this field. The results obtained may contribute to a better understanding of related post-viral conditions, particularly in the context of identifying potential causal therapies.

Finally, there is a need for public health communication strategies that acknowledge the burden of such conditions. Transparent guidance for families, schools, and clinicians is essential to enhance awareness, reduce stigma, and facilitate the early identification of children who may benefit from evaluation or support (40,50,103,106,125,130).

14. FUTURE PERSPECTIVES

In the short term, a new ethical approval has been obtained to further investigate neutrophil alterations in children with long COVID longitudinally. I would like to continue learning and gain further experience, ideally also within an international research environment.

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16.1. Publications Related to the Thesis

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Head-to-head comparison of influenza vaccines in children: a systematic review and meta-analysis
JOURNAL OF TRANSLATIONAL MEDICINE 22: 1 Paper: 903, 15 p. (2024)
Scopus - Biochemistry, Genetics and Molecular Biology (miscellaneous) Rank: D1
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16.2. Publications not Related to the Thesis

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