An Advisory Committee Review
National Advisory Committee on Immunization (NACI)

Literature Review on Individuals with Neurologic or Neurodevelopment Conditions and Risk of Serious Influenza-Related Complications

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada | Agence de la santé publique du Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Neurologic or neurodevelopment conditions (NNCs) account for a substantial burden of disease globally and in Canada. Based on preliminary reviews of evidence, NACI has included children (since the 2015−2016 influenza season) and adults (since the 2016−2017 influenza season) with NNCs among the high-risk groups for whom influenza vaccination is particularly recommended. The present literature review was conducted to provide a rapid synthesis of the evidence to further inform NACI's assessment regarding the inclusion of individuals with NNCs as a high-risk group for influenza-related complications. Although a large number of studies were identified, the body of evidence related to the risk of serious influenza-related complications in adults and children with NNCs is mostly comprised of descriptive studies (i.e., case series), which are generally considered of lower quality (level III evidence). There was also a lack of clarity in the composition of conditions constituting NNCs in some studies and a lack of consistency across identified studies in the defined lists of specific NNCs investigated. However, the body of evidence appears to suggest consistency in the burden and direction of risk of NNCs in both adults and children for pandemic influenza A(H1N1)pdm09 and seasonal influenza. Overall, studies suggest a relatively high burden of pre-existing NNCs in children and adults who had experienced serious pandemic influenza A(H1N1)pdm09- and seasonal influenza-related complications, such as hospitalization, intensive care unit admission and death. There is also consistent evidence to suggest that pre-existing NNCs increase the risk for these serious influenza-related complications. Limited evidence was identified for influenza-related emergency department presentation, respiratory failure and need for mechanical ventilation. The findings of the present rapid literature review are consistent with the preliminary evidence supporting children and adults with NNCs as groups at risk for influenza-related complications and hospitalization.

I. INTRODUCTION

Background

Neurologic conditions refer to a heterogeneous group of neurologic diseases, disorders, and injuries that can occur in individuals of all ages and affect 3.6 million Canadians living in the community and a further 170,000 Canadians living in long-term care facilities[(1)]. Neurologic conditions have been estimated to account for 6.3% of the global burden of disease as measured by disability-adjusted life years, which is a summary measure of years of life lost due to premature mortality and years of healthy life lost as a result of disability, and 10.9% of the burden of disease in a grouping of high-income countries including Canada[(2)]. As some of the more common neurologic conditions increase with age, both the number of individuals with neurologic conditions and the cost of caring for these individuals are expected to rise with the aging of the Canadian population[(1)].

Seasonal influenza vaccine recommendations for Canada are provided annually by NACI to the Agency. These recommendations are developed using NACI's evidence-based process for developing recommendations[(3)] and are published annually on the Agency's website in the NACI Advisory Committee Statement: Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine (hereafter referred to as the Statement). NACI recommends influenza vaccination for all individuals aged six months or older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk and others as indicated in the Statement[(4)].

In the Statement on Seasonal Influenza Vaccine for 2015−2016, NACI concluded that children and adolescents with neurologic or neurodevelopment conditions (NNCs) should be included among the high-risk groups for whom influenza vaccination is particularly recommended[5]. This decision was informed by data from the Canadian Immunization Monitoring Program Active (IMPACT), which documented that the burden of influenza infection in hospitalized children with NNCs, even those whose conditions do not obviously compromise respiratory function, is significant[6]. In the Statement on Seasonal Influenza Vaccine for 2016−2017, NACI included adults with NNCs among the groups for whom influenza vaccination is particularly recommended, based on a preliminary review of the literature and expert opinion, and consistent with other countries' recommendations at the time[4]. NACI defines NNCs as inclusive of neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders (and, for children, febrile seizures and isolated developmental delay), but excludes migraines and psychiatric conditions without neurologic conditions[4]. These recommendations replaced, but are inclusive of the previous recommendation for people with conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration[5].

Purpose and Objectives

The purpose of the present literature review is to conduct a rapid synthesis of relevant evidence in order to provide an evidence summary to further inform NACI's assessment regarding the inclusion of individuals with NNCs as a high-risk group for influenza-related complications. Specifically, the present literature review aims:

Primary Objectives

1. To determine whether individuals with pre-existing NNCs are at higher risk of serious influenza-related complications (i.e., emergency department [ED] presentation, hospitalization, intensive care unit [ICU] admission, death, respiratory failure and need for mechanical ventilation) compared to healthy individuals when infected with influenza;

2. To determine whether individuals with pre-existing NNCs experience a worsening of their underlying NNC when infected with influenza;

Secondary Objectives

3. To determine whether influenza vaccination in individuals with pre-existing NNCs is effective in preventing influenza infection and its complications in this population; and

4. To determine whether influenza vaccination in individuals with pre-existing NNCs can worsen or attenuate a worsening of their condition when subsequently infected with influenza.

II. METHODS

The present literature review was conducted using a rapid review approach, whereby elements of the full systematic review process have been modified due to time and resource limitations but the modified process remains rigorous and transparent in method.

Search Strategy

MEDLINE (1946 to 25 October 2016) and EMBASE (1974 to 25 October 2016) electronic databases were searched from inception using the following Boolean keyword search string

structure for NNCs with corresponding controlled vocabulary additionally used when applicable: (neuro* [OR synonyms]) AND (condition OR disease OR disorder [OR synonyms]). In order to devise a more sensitive search strategy, the aforementioned search string was supplemented with terms for specific NNCs categorized by primary affected location (e.g., central nervous system, peripheral nervous system, neuromuscular conditions) (see Table A1 in Appendix A). The list of supplemental search terms for specific NNCs was generated from the previous preliminary review summarized in the Statement on Seasonal Influenza Vaccine for 2016−2017[4] and through expert consultation with the NACI Influenza Working Group. A sensitivity-maximizing strategy (i.e., emphasizing comprehensiveness) was developed for MEDLINE. A sensitivity- and precision-maximizing strategy (i.e., emphasizing a balance between comprehensiveness and relevancy) was developed for EMBASE, due to the high number of records retrieved for EMBASE using a sensitivity-maximizing strategy. No publication date restrictions were applied for the database searches, but the searches were restricted to records published in English or French. The full electronic search strategies for MEDLINE and EMBASE are presented in Table A2 of Appendix A.

Identification of Eligible Studies

Studies retrieved from the database searches and handsearching were loaded into RefWorks (ProQuest LLC, Ann Arbor, MI) with duplicate records removed. Record screening and eligibility assessment were performed by a single reviewer. Title and abstract information of studies returned by the database searches were screened for potential eligibility. The full-text of studies deemed potentially eligible after title and abstract screening, or for which insufficient information was available to determine eligibility (e.g., no abstract), were obtained and further reviewed for eligibility.

Studies were included for review if they met the following criteria:

- NNCs assessed in the study population and reported
    - NNCs include, but are not limited to neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders (and, for children, include febrile seizures and isolated developmental delay)
- Laboratory-confirmed pandemic influenza A(H1N1)pdm09, seasonal influenza A (i.e., H1N1 and H3N2) and/or seasonal influenza B infection, or pandemic and/or seasonal influenza vaccination
- Serious influenza-related complications (i.e., ED presentation, hospitalization, ICU admission, death, respiratory failure and need for mechanical ventilation), or recurrence, relapse or worsening of NNC in individuals with a history of given condition as outcomes of interest

Studies were excluded if they met one or more of the following criteria:

- Only investigated migraines, psychiatric conditions without neurologic impairment, or neurologic conditions suspected to be an adverse event associated with influenza vaccination (e.g., Bell's Palsy, Guillain-Barré Syndrome, narcolepsy) in persons with no pre-existing NNC
- Small case series (i.e., less than five total cases), secondary research (e.g., systematic review, meta-analysis), review or opinion
- Non-human study
- Non-English and non-French publication

Handsearching of included studies was performed by checking reference lists for cited articles (backward citation search to identify relevant articles that were cited in the articles identified as

eligible for inclusion in the present review) and the Scopus database for citing articles (forward citation search to identify relevant articles that have subsequently cited the articles identified as eligible for inclusion in the present review) to identify additional relevant publications. Due to time and resource constraints, backward and forward citation handsearching was carried out for a 10% random subset rather than the entirety of eligible studies identified from the database searches.

To capture all possible literature investigating NNCs and serious influenza-related complications, or relevant to the other review objectives, no further eligibility restrictions were imposed on publication type, population characteristics, study design specifics and methods for laboratory confirmation of influenza infection. To address potentially repetitive, duplicate or redundant publications with partial or complete overlap, multiple publications based on related data sets (e.g., same data set or overlapping data sets) were condensed into a single primary reference for the study identification, screening and eligibility assessment process. The primary reference was defined as the publication containing final analysis that superseded interim reports or analysis that is most relevant to the present literature review objectives.

Data Extraction

One reviewer extracted data from the eligible studies into an evidence table using a piloted data abstraction template designed to capture information on study design, population and outcomes of interest, as well as any information as appropriate on influenza virus type or subtype, influenza vaccine formulation, influenza season, participants' age group and method of influenza virus testing. A second reviewer independently validated the abstracted data with any disagreements or discrepancies resolved by discussion and consensus.

Qualitative Synthesis

Narrative synthesis of the information extracted from the included studies was used to explore overall patterns in the data, including similarities and differences by age group (children and adults), influenza type (pandemic and seasonal) and outcome (ED presentation, hospitalization, ICU admission, death, respiratory failure and need for mechanical ventilation). Pediatric and adult age ranges were defined according to the age group delineations used in the Statement (i.e., younger than 18 years of age for children and 18 years of age and older for adults)[4]. For studies that did not separately report frequencies of pre-existing NNCs by age group, a study population comprised of at least 70% children or adults was respectively categorized as "predominantly children" or "predominantly adults" to facilitate qualitative synthesis. Otherwise, the study population was categorized as having a "mixture of children and adults." Heterogeneously defined NNCs and outcomes of included studies were grouped by similarity of definition to facilitate qualitative synthesis.

Descriptive analysis was performed to summarize:

- The average proportion of individuals with NNCs among those who had experienced a serious influenza-related complication;
- The average proportion of individuals with NNCs among those who had experienced a serious influenza-related complication and who also had at least one study-defined risk factor for influenza-related complications; and
- The direction, size and statistical significance of reported effect estimates (e.g., odds ratio [OR], relative risk [RR]) from analytical studies in relation to the literature review objectives.

The average proportions of individuals with NNCs were calculated as weighted arithmetic means for each age group, influenza type and outcome combination and provide an indication of the burden of NNCs in individuals that experienced serious influenza-related complications.

Methodological Quality Assessment

The methodological quality of studies was assessed independently by two reviewers using the design-specific criteria by Harris et al. (2001) adopted by NACI for rating the internal validity of individual studies (see Table B1 in Appendix B)[7]. Included studies with study designs that are not covered by Harris et al. (e.g., case series, self-controlled case series, non-randomized controlled or uncontrolled trials) were not rated.

III. RESULTS

The study identification and selection process and study details are summarized in section III.1. Evidence relating to the primary literature review objectives (objectives 1 and 2) is presented in sections III.2 through III.5, including evidence assessing pre-existing NNCs as a risk factor for serious influenza-related complications (sections III.2 to III.4) and evidence investigating the impact of influenza infection on the disease course of pre-existing NNCs (section III.5). Evidence relating to the secondary literature review objectives (objectives 3 and 4) is presented in sections III.6 and III.7, including studies investigating the effect of influenza vaccination in preventing influenza infection and its complications in individuals with pre-existing NNCs (section III.6) and studies assessing the impact of influenza vaccination on the disease course of pre-existing NNCs (section III.7).

III.1 Study Inclusion and Characteristics

The study identification, screening and eligibility assessment process is summarized visually in Appendix C. Database searches and subsequent handsearches yielded a total of 1624 records. Following removal of duplicates, 1399 records were retained for title and abstract screening. Full-text screening of 306 records found 146 studies to be eligible for inclusion in the qualitative synthesis[6, 8-152]. Of the 146 studies included for review, 26 were identified by handsearching[9, 12, 20, 33, 34, 39, 40, 49-51, 62, 69, 81, 85, 87, 111, 117, 119, 126, 129, 137, 140-142, 145, 147]. All included studies were English language publications, with the exception of three published in French[47, 52, 57]. Abstracted study data are presented in the evidence table in Appendix D. For multiple publications based on related data sets, abstracted data from six primary references included for review[38, 71, 73, 92, 106, 139] were supplemented with partial, non-duplicative data from seven related publications as indicated in Appendix D[153-159].

Case series (level III evidence) comprise 132 of 146 studies retained for qualitative synthesis[6, 8-34, 37-41, 43-50, 52-57, 61-77, 81-93, 96-98, 100-104, 106-152], including four self-controlled case series[14, 45, 135, 152]. Nine studies used the case-control design[35, 36, 42, 51, 58-60, 78, 79] (level II-2 evidence) and one study used a case-cohort design (level II-2 evidence) to analyze pooled data from two prospective cohort studies and a randomized controlled trial[80]. A total of four clinical trials were included for review, including two double-blind, non-randomized, placebo-controlled trials (level II-1 evidence) [95, 99], one double-blind, randomized, placebo-controlled trial (level I evidence)[105] and one uncontrolled trial (level III evidence)[94]. See Table B2 in Appendix B for further information on the levels of evidence based on research design.

The limited number of included studies with evaluable study designs as outlined by Harris et al. were rated "fair" or better[35, 36, 42, 51, 58-60, 78-80, 105]. For case series, in addition to potential biases and limitations inherent to the descriptive nature of this design, specific concerns regarding possible selection bias or misclassification bias were noted. For example, a minority of case series explicitly indicated the recruitment of consecutive cases[16, 43, 48, 50, 86, 87, 92, 100, 107, 113, 122, 123, 141]; only a few studies among the many studies that included different influenza virus testing methods with varying degrees of sensitivity and specificity applied additional validation methods[71, 87, 96, 97, 117, 140, 149]; and some studies used registry or administrative data sets potentially containing a proportion of non-laboratory-confirmed influenza illness[49, 124]. For all other study designs that were not evaluated with the Harris et al. criteria, no critical flaws were noted besides the intrinsic limitations of those designs.

III.2 Proportion of NNCs in Individuals with Serious Laboratory-Confirmed Influenza-Related Complications

The majority of studies included for review were descriptive studies (i.e., case series) that characterized underlying study-defined risk factors for influenza-related complications, including NNCs as a broad categorization of conditions, of individuals with serious influenza-related complications. Reported risk factors varied in definition across studies. Cases recruited as part of case-control studies were also included for this qualitative synthesis. The proportion of NNCs in individuals with laboratory-confirmed influenza-related hospitalization is presented in Table 1, ICU admission in Table 2 and death in Table 3. There was a wide range of reported proportions of persons with NNCs across studies.

III.2.1 Hospitalization

The mean proportion of children with NNCs was 13.2% among pediatric pandemic influenza A(H1N1)pdm09-related hospitalizations (n=30 studies; range: 3.6−33.7%)[10, 16, 23, 33, 35-37, 41, 46, 49, 63, 64, 68, 71, 72, 78, 81-83, 85, 88, 103, 111, 116, 119, 130, 134, 136, 144, 149] and 11.2% among pediatric seasonal influenza-related hospitalizations (n=16 studies; range: 3.3−28.1%)[6, 12, 16, 31, 38, 49, 64, 79, 101, 103, 117, 119, 126, 129, 143, 147]. All comparative studies of pandemic and seasonal influenza reported statistically similar proportions of pediatric pandemic and seasonal influenza-related hospitalizations with NNCs[16, 35, 49, 64, 103, 119, 144]. Of the children with at least one study-defined risk factor for influenza-related complications, almost a quarter of children on average who were hospitalized for influenza infection had NNCs as a risk factor (mean proportion of 24.2% for pandemic influenza and 25.8% for seasonal influenza).

The mean proportion of adults with NNCs was found to be 8.9% among adult pandemic influenza-related hospitalizations (n=6 studies; range: 4.4−14.0%)[19, 60, 68, 86, 120, 134] and 13.3% among adult seasonal influenza-related hospitalizations (n=3 studies; range: 2.5−14.8%)[59, 91, 120]. Unlike pediatric studies, a comparative study reported that a statistically greater proportion of adults who experienced seasonal influenza-related hospitalizations had pre-existing NNCs compared to adults that experienced pandemic influenza-related hospitalizations[120]. A comparative study of a mixture of pediatric and adult hospitalizations for pandemic and seasonal influenza infection found statistically similar proportions of individuals with NNCs [84]. Of the adults with at least one study-defined risk factor for influenza-related complications, on average, 12.0% of adults who were hospitalized for pandemic influenza infection and 17.1% of adults who were hospitalized for seasonal influenza infection had NNCs as a risk factor.

Table 1: Proportion of NNCs in individuals with laboratory-confirmed influenza-related hospitalization

Age group	Pandemic influenza A(H1N1)pdm09					Seasonal influenza				
	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference
Children	3.6	25.5	14.3	55	(64)	3.3	25.2	13.1	3157	(32)*
	4.2	37.5	11.1	48	(36)	3.4	20.7	16.7	116	(147)
	4.2	40.3	10.3	72	(81)	4.9	30.2	16.4	182	(117)
	5.8	27.5	21.1	517	(46)	5.2	25.9	20.1	1308	(129)
	6.6	41.0	16.0	61	(33)**	5.3	36.4	14.6	132	(126)
	6.6	44.7	14.8	197	(111)	7.2	34.6	20.7	279	(119)***
	6.8	33.6	20.4	482	(119)***	8.6	53.9	16.0	230	(143)*
	8.3	38.7	21.4	326	(63)	8.6	36.9	23.3	325	(12)
	8.5	42.6	20.0	94	(149)	10.1	32.9	30.8	79	(64)
	8.6	38.0	22.6	221	(82)	11.7	42.0	27.8	505	(101)
	8.6	33.6	25.5	245	(85)***	11.9	48.7	24.6	745	(38)**
	8.6	48.7	17.6	478	(136)**	13.0	NR	NA	200	(103)
	10.1	40.4	25.0	99	(35)	14.0	49.6	28.2	10173	(49)
	11.0	39.5	27.8	200	(41)	14.7	56.0	26.3	1991	(6)
	11.7	40.3	29.0	77	(72)	17.0	38.5	44.2	135	(78)
	11.9	NR	NA	176	(103)	28.1	51.7	54.3	89	(16)**
	12.9	45.8	28.2	821	(37)					
	13.4	42.7	31.4	82	(83)					
	13.4	49.0	27.4	506	(71)					
	13.6	58.7	23.1	1265	(144)					
	14.0	70.0	20.0	50	(10)					
	14.0	47.7	29.4	86	(134)					
	14.1	59.6	23.6	9837	(49)					
	14.2	43.3	32.7	120	(130)					
	14.4	47.0	30.7	215	(23)					
	15.9	47.7	33.3	195	(79)					
	17.1	61.4	27.8	345	(88)					
	20.0	59.8	33.4	122	(68)					
	24.1	66.1	36.5	307	(16)**					
	33.7	NR	NA	98	(116)**					
	Weighted arithmetic mean: **13.2**		**24.2**			Weighted arithmetic mean: **11.2**		**25.8**		
Adults	4.4	62.8	7.1	699	(60)**	2.5	NR	NA	471	(59)
	4.8	54.8	8.8	62	(86)	8.7	72.9	11.7	598	(91)
	9.0	83.3	10.8	150	(68)	14.8	84.1	17.6	5270	(120)
	9.4	79.7	11.8	4962	(120)					
	11.1	69.1	16.1	81	(19)**					
	14.0	76.3	18.3	169	(134)					
	Weighted arithmetic mean: **8.9**		**12.0**			Weighted arithmetic mean: **13.3**		**17.1**		
Mixture†	3.2	NR	NA	342	(18)	10.5	75.0	14.0	76	(84)
	5.9	57.9	10.2	321	(58)	12.0	NR	NA	276	(109)
	5.9	50.3	11.8	2021	(27)					
	11.1	62.1	17.9	926	(141)					
	14.7	51.0	28.8	102	(84)					

Abbreviations: NA, not available; NNCs, neurologic or neurodevelopment conditions; NR, not reported.

* Includes pandemic influenza A(H1N1)pdm09 cases.

** Predominantly children or predominantly adults, defined as a study population having at least 70% of children or adults, respectively.

[***] Total cases differed for the calculation of proportion of individuals with risk factors for influenza-related complications and for the proportion with NNCs.
[†] Defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").

III.2.2 ICU Admission

The mean proportion of children with NNCs was found to be 27.5% among pediatric pandemic influenza A(H1N1)pdm09-related ICU admissions (n=20 studies; range: 12.3−80.0%)[10, 16, 23, 33, 41, 46, 70, 73, 82, 87, 88, 102, 103, 118, 128, 132, 136, 142, 144, 149] and 25.0% among pediatric seasonal influenza-related ICU admissions (n=9 studies; range: 10.0−34.0%)[6, 69, 89, 96, 102, 103, 137, 138, 144]. Two comparative studies reported a statistically similar proportion of children who had pre-existing NNCs among those that experienced influenza-related ICU admissions due to pandemic and seasonal influenza[102, 103]. The mean proportions of children with NNCs among those that experienced pandemic and seasonal influenza-related ICU admissions were both over two-fold higher than pediatric pandemic and seasonal influenza-related hospitalizations (27.5% vs. 13.2% for pandemic influenza and 25.0% vs. 11.2% for seasonal influenza). Of the children with at least one study-defined risk factor for influenza-related complications, about 40% of children on average who were admitted to ICU for influenza infection had NNCs as a risk factor (mean proportion of 39.9% for pandemic influenza and 41.1% for seasonal influenza).

The mean proportion of adults with NNCs was found to be 16.7% among adult pandemic influenza-related ICU admissions (n=7 studies; range: 5.9−30.0%)[19, 43, 57, 62, 73, 113, 114]. Only one study reported the proportion of adult seasonal influenza-related ICU admissions with NNCs, which was determined to be 0.9%[62]. Two studies found a statistically higher proportion of adult pandemic influenza-related ICU admissions with NNCs compared to seasonal influenza[39, 62]. The mean proportion of adult pandemic influenza-related ICU admissions with NNCs was higher than adult pandemic influenza-related hospitalizations with NNCs (16.7% vs. 8.9%), but comparable to adult seasonal influenza-related hospitalizations with NNCs (16.7% vs.13.3%). Of the adults with at least one study-defined risk factor for influenza-related complications, on average, 18.3% of adults who were admitted to ICU for pandemic influenza infection had NNCs as a risk factor.

The mean proportions of individuals with NNCs among pediatric pandemic and seasonal influenza-related ICU admissions were approximately 1.5-fold higher than that observed among adult pandemic influenza-related ICU admissions (27.5% and 25.0% vs. 16.7%, respectively).

Table 2: Proportion of NNCs in individuals with laboratory-confirmed influenza-related ICU admission

Age group	Pandemic influenza A(H1N1)pdm09					Seasonal influenza				
	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference
Children	12.3	50.6	24.4	81	(142)	10.0	55.0	18.2	20	(138)
	13.3	63.3	21.1	30	(132)	18.5	59.3	31.3	27	(69)[**]
	14.3	57.1	25.0	14	(33)[*,**]	22.5	53.1	42.4	160	(89)[**]
	15.7	56.9	27.6	51	(46)	22.7	50.0	45.5	22	(96)
	18.8	NR	NA	32	(103)	23.4	58.1	40.2	167	(144)
	19.0	64.3	29.6	42	(136)[*]	24.1	40.7	59.1	54	(102)
	20.0	68.6	29.1	185	(144)	25.8	NR	NA	31	(103)

Age group	Pandemic influenza A(H1N1)pdm09					Seasonal influenza				
	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference
	22.8	70.2	32.5	57	(73)	28.0	68.2	41.0	261	(6)
	23.8	61.9	38.5	21	(23)	34.0	76.6	44.4	47	(137)
	24.1	75.9	31.7	83	(70)					
	26.7	64.4	41.4	45	(102)					
	29.2	72.9	40.0	96	(88)**					
	30.0	83.3	36.0	30	(128)					
	31.4	70.0	44.8	838	(118)*					
	33.3	66.7	50.0	6	(149)					
	37.5	71.3	52.6	80	(16)*					
	38.5	92.3	41.7	13	(87)					
	40.0	90.0	44.4	10	(82)					
	45.5	90.9	50.0	11	(41)					
	80.0	100.0	80.0	5	(10)					
	Weighted arithmetic mean: **27.5**		**39.9**			Weighted arithmetic mean: **25.0**		**41.1**		
Adults	5.9	64.7	9.1	17	(113)*	0.9	79.1	1.1	115	(62)*
	15.4	84.6	18.2	13	(57)*					
	15.5	98.2	15.8	168	(73)*					
	18.4	79.6	23.1	49	(114)*					
	18.8	65.6	28.6	32	(43)*					
	19.1	78.8	24.3	47	(62)*,***					
	30.0	100.0	30.0	10	(19)**					
	Weighted arithmetic mean: **16.7**		**18.8**							
Mixture†	6.4	61.7	10.3	47	(58)	NA				
	14.0	90.0	15.6	50	(84)**,‡					
	17.9	67.2	26.7	67	(68)**					

Abbreviations: NA, not available; NNCs, neurologic or neurodevelopment conditions; NR, not reported.

* Predominantly children or predominantly adults, defined as a study population having at least 70% of children or adults, respectively.

** Includes non-ICU deaths.

*** Total cases differed for the calculation of proportion of individuals with risk factors for influenza-related complications and for the proportion with NNCs.

† Defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").

‡ Includes seasonal influenza A(H1N1)pdm09 cases.

III.2.3 Influenza-Related Death

The mean proportion of children with NNCs was found to be 42.2% among pediatric pandemic influenza A(H1N1)pdm09-related deaths (n=14 studies; range: 0.0−100.0%)[8, 22, 23, 37, 46, 53, 70, 71, 85, 88, 106, 108, 121, 130] and 32.1% among pediatric seasonal influenza-related deaths (n=6 studies; range: 24.0−80.0%)[6, 21, 39, 89, 137, 150]. One comparative study reported statistically similar proportions of children with pre-existing NNCs among pediatric pandemic and seasonal influenza-related deaths[39]. The mean proportions of both pediatric pandemic and seasonal influenza-related deaths with NNCs were higher than the mean proportion with NNCs observed for pediatric ICU admissions (42.2% vs. 27.5% for pandemic influenza and 32.1% vs. 25.0% for seasonal influenza) and approximately three-fold higher than pediatric hospitalizations (42.2% vs. 13.2% for pandemic influenza and 32.1% vs. 11.2% for seasonal influenza). On average, of

the children with at least one study-defined risk factor for influenza-related complications, more than half of children who died from influenza infection had NNCs as a risk factor (mean proportion of 61.5% for pandemic influenza and 57.8% for seasonal influenza).

The mean proportion of adults with NNCs was found to be 18.2% among adult pandemic influenza-related deaths (n=7 studies; range: 6.7−25.0%)[17, 53, 84, 106, 112, 121, 125]. No studies included for review reported the proportion of adult seasonal influenza-related deaths with NNCs; however, one study compared observed adult pandemic influenza-related deaths to seasonal influenza-related death registry data and found no statistically significant difference in the proportions with NNCs[112]. The mean proportion of adult pandemic influenza-related deaths with NNCs was somewhat higher than for ICU admissions (18.2% vs. 16.7%) and two-fold higher than for hospitalizations (18.2% vs. 8.9%). Although lower than that observed in children, of the adults with at least one study-defined risk factor for influenza-related complications, nearly a quarter of adults on average who died from pandemic influenza infection had NNCs as a risk factor (mean proportion of 24.2%).

The mean proportions of children who had pre-existing NNCs among those who died with pandemic (42.2%) and seasonal (32.1%) influenza were close to two-fold higher than the mean proportion observed for adult pandemic influenza-related deaths (18.2%).

Table 3: Proportion of NNCs in individuals with laboratory-confirmed influenza-related death

Age group	Pandemic influenza A(H1N1)pdm09					Seasonal influenza				
	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference
Children	0.0	80.0	0.0	5	(8)	24.0	45.9	52.2	146	(39)
	20.0	80.0	25.0	25	(70)	32.7	57.1	57.4	794	(150)*
	25.7	74.3	34.6	35	(37)	32.9	53.0	62.0	149	(21)
	26.8	34.1	78.6	41	(108)	33.3	80.0	41.7	15	(89)
	30.8	69.2	44.4	13	(85)	57.1	64.3	88.9	14	(6)
	34.9	62.8	55.6	43	(121)	80.0	100.0	80.0	5	(137)
	43.5	67.6	64.3	336	(22)					
	45.5	90.9	50.0	11	(130)					
	54.2	68.8	78.8	48	(53)					
	54.3	78.6	69.1	70	(106)					
	55.6	88.9	62.5	9	(88)					
	60.0	100.0	60.0	5	(46)					
	60.0	80.0	75.0	5	(71)					
	100.0	100.0	100.0	5	(23)					
	Weighted arithmetic mean: **42.2**		**61.5**			Weighted arithmetic mean: **32.1**		**57.8**		
Adults	6.7	93.3	7.1	15	(84)*	NA				
	11.6	79.7	14.5	276	(53)**					
	17.9	74.9	23.9	301	(17)**,***					
	18.5	73.6	25.1	254	(121)					
	20.4	70.6	29.0	357	(106)**					
	21.8	72.1	30.2	308	(112)**					
	25.0	62.5	40.0	8	(125)**					
	Weighted arithmetic mean: **18.2**		**24.2**							
Mixture†	6.3	NR	NA	64	(18)	NA				

Age group	Pandemic influenza A(H1N1)pdm09					Seasonal influenza				
	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference	% with NNCs in total cases	% with ≥1 risk factor in total cases	% with NNCs in cases with ≥1 risk factor	Total cases	Reference
	6.7	60.0	11.1	15	(58)					
	20.0	77.1	25.9	35	(141)					
	21.1	68.4	30.8	19	(68)					

Abbreviations: NA, not available; NNCs, neurologic or neurodevelopment conditions; NR, not reported.
* Includes pandemic or seasonal influenza A(H1N1)pdm09 cases.
** Predominantly children or predominantly adults, defined as a study population having at least 70% of children or adults.
*** Total cases differed for the calculation of proportion of individuals with risk factors for influenza-related complications and for the proportion with NNCs.
† Defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").

III.2.4 Other Complications

The review identified a relative paucity of evidence for influenza-related ED visit, hospitalization with respiratory failure, hospitalization requiring mechanical ventilation, and for other complications concurrent with hospitalization, such as influenza-related hospitalization with neurologic complication (i.e., neurologic manifestation of influenza infection including but not limited to seizure, encephalopathy or encephalitis) or pneumonia. The proportion with NNCs ranged from 4.3%[47] to 15.0%[98] among children and was observed to be 1.0%[113] among adults presenting to EDs for influenza infection. One study reported 9.7% of pediatric cases of pandemic influenza-related hospitalizations with respiratory failure had intellectual disability and 3.2% had a history of epilepsy[146]. Two studies reported 34.6%[6] and 35.5%[49] of individuals with seasonal influenza-related hospitalizations requiring mechanical ventilation had NNCs and one study reported 17.9% of individuals with pandemic influenza-related hospitalizations requiring mechanical ventilation had NNCs[141]. About 28% of children hospitalized with pandemic influenza A(H1N1)pdm09-related neurologic complications had pre-existing NNCs[104]. Among adults who had experienced influenza-related hospitalization with pneumonia, 4.0% of those with pandemic influenza infection and 21.2% of those with seasonal influenza infection had NNCs; this difference in proportions was statistically significant (p=0.002)[123]. Only 1.9% of children who had experienced pandemic influenza-related hospitalization with pneumonia had NNCs[81].

III.3 Proportion of Specific NNCs in Individuals with Serious Laboratory-Confirmed Influenza-Related Complications

Some studies included for review investigated more specific NNCs instead of or in addition to NNCs as a broad categorization. These specific conditions may be subcategorizations of NNCs by primary affected location (e.g., central nervous system) or conditions within those subcategorizations (e.g., cerebral palsy, neurodevelopmental conditions). The proportions of specific NNCs in individuals with serious laboratory-confirmed influenza-related complications, including hospitalization, ICU admission and death, are aggregated in Tables 4 to 6 for children and Tables 7 to 9 for adults, with the more frequently identified specific NNCs indicated narratively for both age groups. For both children and adults, there were more study data available for proportions with specific NNCs for serious pandemic influenza A(H1N1)pdm09-

related complications compared to serious seasonal influenza-related complications. As with more broadly defined NNCs, there was a wide range of reported proportions of persons with specific NNCs across studies.

III.3.1 Children

For children, the proportions of specific NNCs are summarized for laboratory-confirmed influenza-related hospitalization in Table 4, ICU admission in Table 5 and death in Table 6. The more frequently identified specific NNCs in children across the aforementioned serious laboratory-confirmed influenza-related complications were cerebral palsy, neurodevelopmental conditions (developmental delay), neuromuscular conditions and seizures (epilepsy and febrile seizure).

Table 4: Proportion of specific NNCs in children with laboratory-confirmed influenza-related hospitalization

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Central nervous system	NA			3.6	56	(93)
Cerebral palsy	1.9	103	(104)	2.0	505	(101)
	2.3	43	(77)	2.5	325	(12)
	3.0	197	(111)	2.6	77	(25)
				4.8	745	(38)
				7.9	89	(16)*
Cerebral palsy or developmental delay	0.7	148	(151)	NA		
	6.7	506	(71)			
	11.9	345	(88)			
Cerebrovascular disease	NA			NA		
Stroke	1.0	98	(116)*	NA		
Congenital anomalies, defects or malformations of the brain and spine	0.8	2901	(124)	NA		
Hydrocephalus	NA			0.6	505	(101)
				3.6	745	(38)
Spina bifida	NA			0.9	325	(12)
Encephalopathy	1.2	506	(71)	0.4	745	(38)
	3.2	63	(26)	1.2	505	(101)
Neurodevelopmental conditions	8.1	86	(134)	23.6	89	(16)*
	17.6	119	(40)*			
	18.6	307	(16)*			
Developmental delay	3.4	263	(54)	6.2	792	(31)
				7.1	2709	(44)
Developmental delay with seizures, hydrocephalus, microcephaly, or neuromuscular abnormality	NA			3.6	505	(101)
Developmental delay without other abnormality	NA			0.6	505	(101)
Intellectual disability	NA			3.9	77	(25)
Seizures	2.5	197	(111)	2.4	505	(101)
	3.8	263	(54)	4.5	4015	(44)
	6.7	75	(74)*	4.6	325	(12)
	7.0	86	(134)	5.0	745	(38)
	9.0	345	(88)	8.9	123	(75)
	9.0	446	(127)	10.1	89	(16)*
	10.7	122	(68)			

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
	12.1	307	(16)*			
	16.5	103	(104)			
Epilepsy	3.3	543	(139)*	NA		
	3.4	2901	(124)			
	3.8	506	(71)			
	8.7	149	(28)			
	11.8	17	(52)			
	13.3	98	(116)*			
Febrile seizure	0.9	326	(63)	1.4	2709	(44)
	1.3	75	(74)*	1.9	745	(38)
	11.2	98	(116)*			
Seizures or epilepsy	2.8	326	(63)	NA		
Neuromuscular conditions	1.0	197	(111)	1.2	505	(101)
	1.1	263	(54)	4.1	2709	(44)
	1.1	543	(139)*	4.6	830	(31)*
	1.9	103	(104)	8.8	80	(110)
	4.6	43	(77)	14.2	922	(20)**
	6.8	133	(140)	18.0	133	(140)
	7.1	126	(28)	18.2	110	(90)
	7.7	364	(127)			
	9.3	75	(74)*			
	9.3	86	(134)			
	10.3	155	(56)			
	10.4	67	(110)			
	10.4	115	(97)			
	10.7	122	(68)			
Hypotonia	NA			0.8	745	(38)
Muscular dystrophy	NA			0.4	745	(38)
				0.9	325	(12)
Myasthenia gravis	2.0	98	(116)*	NA		

Abbreviations: NA, not available; NNC, neurologic or neurodevelopment condition.
* Predominantly children, defined as a study population having at least 70% of children.
** Includes pandemic influenza A(H1N1)pdm09 cases.

Table 5: Proportion of specific NNCs in children with laboratory-confirmed influenza-related ICU admission

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Central nervous system	3.3	30	(115)	8.7	23	(115)
	19.3	83	(70)			
Cerebral palsy	12.5	80	(16)*	4.5	22	(96)
	19.3	57	(73)	5.0	160	(89)
	60.0	5	(10)	7.4	27	(69)**
Cerebral palsy or developmental delay	21.9	96	(88)**	NA		
	27.2	265	(42)**			
Congenital anomalies, defects or malformations of the brain and spine	NA			NA		
Microcephaly	NA			2.5	160	(89)
Encephalopathy	NA			1.9	160	(89)
Neurodevelopmental conditions	6.7	30	(132)	15.4	13	(66)
	32.0	25	(40)**			
	30.0	80	(16)*			
	57.3	89	(11)			

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Developmental delay	10.3	116	(54)	8.0	125	(31)
				8.8	160	(89)
				13.6	22	(96)
Down syndrome	NA			7.4	27	(69)**
Intellectual disability	NA			5.0	20	(138)
Seizures	6.7	30	(132)	7.7	13	(66)
	12.1	116	(54)	9.1	22	(96)
	14.6	96	(88)**	11.9	160	(89)
	17.5	57	(73)			
	21.3	80	(16)*			
	40.0	5	(10)			
	66.7	6	(111)			
Epilepsy	43.8	16	(139)*,**	3.7	27	(69)**
Neuromuscular conditions	0.9	116	(54)	11.3	141	(31)
	2.4	83	(70)	36.4	44	(51)
	16.3	147	(50)	42.1	19	(90)
	18.8	16	(139)*,**			
Peripheral nervous system	NA			NA		
Neuropathy	28.6	7	(145)	5.0	20	(138)

Abbreviations: NA, not available; NNC, neurologic or neurodevelopment condition.
* Predominantly children, defined as a study population having at least 70% of children.
** Includes non-ICU deaths.

Table 6: Proportion of specific NNCs in children with laboratory-confirmed influenza-related death

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Central nervous system	NA			NA		
Cerebral palsy	15.2	336	(22)	6.7	15	(89)
	31.4	70	(106)	9.4	149	(21)
				9.8	794	(150)*
Cerebral palsy or developmental delay	44.4	9	(88)	NA		
Cerebrovascular disease	NA			NA		
Stroke	0.0	43	(121)	NA		
Congenital anomalies, defects or malformations of the brain and spine	13.0	23	(124)	NA		
Hydrocephaly	4.8	336	(22)	NA		
Microcephaly	NA			6.7	15	(89)
Neurodevelopmental conditions	40.8	336	(22)	20.5	146	(39)
	52.1	48	(53)	26.7	792	(150)*
	61.1	36	(29)			
	70.0	10	(11)			
Autism	0.9	336	(22)	NA		
Developmental delay	30.2	43	(121)	6.7	15	(89)
				28.2	149	(21)
Intellectual disability	33.0	336	(22)	NA		
Seizures	15.2	46	(30)	11.6	146	(39)
	25.0	48	(53)	15.4	149	(21)
	25.6	43	(121)	15.9	794	(150)*
				20.0	15	(89)
Epilepsy	22.0	336	(22)	NA		
	30.4	23	(124)			

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
	31.4	70	(106)			
	50.0	2	(139)**			
Febrile seizure	14.6	41	(108)	NA		
Neuromuscular conditions	0.0	2	(139)**	2.1	146	(39)
	2.7	336	(22)	3.1	794	(150)*
	6.3	48	(53)			
	18.6	43	(121)			
	21.1	57	(50)			
Muscular dystrophy	1.8	336	(22)	NA		

Abbreviations: NA, not available; NNC, neurologic or neurodevelopment condition.
* Includes pandemic influenza A(H1N1)pdm09 cases.
** Predominantly children, defined as a study population having at least 70% of children.

III.3.2 Adults

For adults, the proportions of NNCs are summarized for laboratory-confirmed influenza-related hospitalization in Table 7, ICU admission in Table 8 and death in Table 9. The more frequently identified specific NNCs in adults with serious laboratory-confirmed influenza-related complications were neurodevelopmental conditions, neuromuscular conditions (myasthenia gravis [MG]), seizures and cerebrovascular disease (stroke and transient ischemic attack [TIA]).

Table 7: Proportion of specific NNCs in adults with laboratory-confirmed influenza-related hospitalization

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Central nervous system	NA			NA		
Cerebrovascular disease	1.6	62	(86)	1.4	276	(109)*
				11.4	79	(148)
Stroke	2.0	50	(48)*	NA		
Stroke or TIA	NA			25.8	132	(13)
Congenital anomalies, defects or malformations of the brain and spine	1.1	8548	(124)*	NA		
Neurodegenerative disorder	NA			NA		
Dementia	NA			17.4	132	(13)
Neurodevelopmental conditions	5.9	169	(134)	NA		
	12.5	96	(34)*,**			
Seizures	1.6	62	(86)	3.7	5270	(120)
	3.3	1877	(127)***			
	3.3	150	(68)			
	3.8	4962	(120)			
	4.7	169	(134)			
Epilepsy	1.1	805	(139)	NA		
	1.9	8548	(124)*			
	2.8	530	(28)***			
Neuromuscular conditions	0.7	805	(139)	3.8	79	(148)
	3.3	483	(28)***	4.9	123	(67)
	3.6	1522	(127)***	5.3	5270	(120)
	4.0	150	(68)	7.6	2791	(31)
	4.4	4962	(120)	13.8	123	(61)
	4.8	105	(61)			

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
	6.5	169	(134)			

Abbreviations: NA, not available; NNC, neurologic or neurodevelopment condition.
* Mixture of children and adults, defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").
** Hospitalization with pneumonia.
*** Predominantly adults, defined as a study population having at least 70% of adults.

Table 8: Proportion of specific NNCs in adults with laboratory-confirmed influenza-related ICU admission

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Central nervous system	NA			NA		
Cerebral palsy	6.3	32	(43)*	NA		
	9.5	168	(73)*			
Cerebrovascular disease	4.8	168	(73)*	NA		
	5.0	40	(9)*			
Ischemic stroke	3.1	32	(43)*	NA		
Neurodevelopmental conditions	10.1	89	(134)*	NA		
Seizures	6.5	751	(127)*	NA		
	7.7	168	(73)*			
	7.9	89	(134)*			
	12.1	33	(107)*			
Epilepsy	0.0	76	(139)**	NA		
	6.3	32	(43)*			
Neuromuscular conditions	1.8	57	(65)***	1.1	349	(92)*
	2.7	1120	(55)*	4.3	23	(115)*
	3.1	32	(122)*	9.9	536	(31)
	3.7	648	(92)*			
	4.9	627	(127)*			
	5.3	76	(139)**			
	5.7	122	(24)*			
	6.7	30	(115)*			
	10.1	89	(134)*			
Myasthenia gravis	3.1	32	(43)*	NA		

Abbreviations: NA, not available; NNC, neurologic or neurodevelopment condition.
* Predominantly adults, defined as a study population having at least 70% of adults.
** Includes non-ICU deaths.
*** Mixture of children and adults, defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").

Table 9: Proportion of specific NNCs in adults with laboratory-confirmed influenza-related death

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Central nervous system	NA			NA		
Cerebral palsy	3.8	183	(30)*	NA		
	4.8	357	(106)			
Cerebral palsy or developmental delay	7.1	308	(112)*	NA		

Specific NNC	Pandemic influenza A(H1N1)pdm09			Seasonal influenza		
	% with specific NNC	Total cases	Reference	% with specific NNC	Total cases	Reference
Cerebrovascular disease	NA			NA		
Stroke	3.9	254	(121)	2.6	76	(131)
Stroke or TIA	4.8	357	(106)	44.4	27	(13)
Congenital anomalies, defects or malformations of the brain and spine	4.6	259	(124)*	NA		
Neurodegenerative disorder	NA			NA		
Dementia	NA			18.5	27	(13)
Neurodevelopmental conditions	5.8	276	(53)	NA		
Developmental delay	3.9	254	(121)	NA		
	9.5	357	(106)			
Down syndrome	2.3	308	(112)*	NA		
Intellectual disability	12.5	8	(125)*	NA		
Seizures	2.9	137	(30)	NA		
	4.3	276	(53)			
	6.3	254	(121)			
Epilepsy	0.0	16	(139)	NA		
	2.9	308	(112)*			
	3.1	259	(124)*			
	5.9	357	(106)			
Neuromuscular conditions	1.1	276	(53)	1.9	105	(92)*
	1.4	357	(106)			
	3.2	308	(112)*			
	4.3	141	(92)*			
	8.3	254	(121)			
	10.0	20	(24)*			
	12.5	16	(139)			
Myasthenia gravis	12.5	8	(125)*	NA		
Spinal muscular atrophy	0.8	357	(106)	NA		

Abbreviations: NA, not available; NNC, neurologic or neurodevelopment condition.
* Predominantly adults, defined as a study population having at least 70% of adults.

III.4 Risk of Serious Laboratory-Confirmed Influenza-Related Complications in Individuals with NNCs

Among the studies included for review, 47 studies assessed the association between NNCs or specific NNCs and serious influenza-related complications, such as hospitalization, ICU admission, death, respiratory failure and need for mechanical ventilation[6, 11, 13, 18, 19, 22, 27, 31-34, 37, 38, 40-42, 46, 49, 50, 54, 58-60, 65, 68, 70, 71, 73, 78, 79, 82, 85, 88, 90, 92, 106, 109, 112, 114, 118, 119, 127, 136, 139, 141, 144, 148]. No studies were identified that examined NNCs as a risk factor for influenza-related ED visit. The association of NNCs with influenza-related hospitalization was predominantly evaluated in case-control studies while associations with other serious influenza-related complications, such as ICU admission, death, respiratory failure, or need for mechanical ventilation were primarily evaluated in descriptive studies (i.e., case series).

III.4.1 Hospitalization

Ten studies evaluated NNCs as a risk factor for influenza-related hospitalization (Table 10)[27, 54, 58-60, 78, 79, 82, 109, 148]. All of the studies with available relative effect measures reported an increased risk of influenza-related hospitalization in children and adults with NNCs (i.e., OR or RR > 1) compared to those without the NNC, with most of these associations being statistically significant.

Specific NNCs identified as statistically significant risk factors for influenza-related hospitalization include neurologic conditions[27, 78, 79, 82] and seizure disorder[54] in children and neuromuscular conditions in adults[148]. Developmental delay and neurocognitive conditions[54] in children and cerebrovascular disease[148] in adults were not identified as statistically significant risk factors for influenza-related hospitalization. Disabling neurologic condition was found to be a statistically significant risk factor in adults for pandemic influenza[60] but not seasonal influenza[59].

Table 10: Risk of laboratory-confirmed influenza-related hospitalization in individuals with NNCs

Influenza type	Age group	NNC	Relative effect measure (95% CI)	Statistical significance (p-value)	Reference
Pandemic influenza A(H1N1)pdm09	Children	Developmental delay	aOR: 2.20 (0.99–4.87)	0.051	(54)
		Neurocognitive condition	NR	NS	(54)
		Neurologic condition	aOR: 3.0 (1.1–8.2)	0.03	(79)
			OR: 15.74 (7.96–31.11)	<0.05	(82)
			aRR: 14.3 (11.8–17.2)	<0.05	(27)
			NR	NS	(54)
		Neuromuscular condition	NR	NS	(54)
		Seizure disorder	aOR: 4.71 (2.11–10.52)	<0.001	(54)
	Adults	Disabling neurologic condition	aOR: 4.0 (1.24–12.99)	0.02	(60)
	Mixture*	Neuromuscular condition	aOR: 22.2 (2.6–186.0)	<0.05	(58)
Seasonal influenza	Children	Neurologic condition	aOR: 17.18 (3.44–85.90)	0.001	(78)
	Adults	Cerebrovascular disease	aOR: 1.42 (0.52–3.85)	0.490	(148)
		Disabling neurologic condition	NR	0.10	(59)
		Neuromuscular condition	aOR: 10.18 (1.30–79.40)	0.027	(148)
	Mixture*	Cerebrovascular disease	aHR: 2.48 (0.88–6.97)	0.084	(109)
		Neurologic condition	aHR: 2.62 (1.68–4.11)	<0.001	(109)

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; OR, odds ratio; NNC, neurologic or neurodevelopment condition; NR, not reported; NS, not significant.
* Defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").

III.4.2 ICU Admission

Twenty-two studies evaluated NNCs as a risk factor for influenza-related ICU admission (Table 11)[6, 19, 31-33, 37, 40-42, 46, 58, 65, 68, 71, 88, 90, 114, 119, 127, 136, 139, 144]. A majority of these studies reported statistically significant and increased risk of ICU admission among hospitalizations for pandemic or seasonal influenza infection for children and adults with NNCs compared to children or adults without the NNC.

Specific NNCs generally identified across studies as statistically significant risk factors for ICU admission among influenza-related hospitalizations in children include neurologic[37, 41, 46, 71, 119, 136, 144], neurodevelopmental[40] and neuromuscular[46] conditions, as well as cerebral palsy or developmental delay among ED presentations[42] and hospitalizations[88], but not seizure disorder[88]. In adults, neurologic[114] and neurocognitive[19] conditions were identified as statistically significant risk factors, but findings were mixed for neuromuscular conditions[31, 127].

Table 11: Risk of laboratory-confirmed influenza-related ICU admission in individuals with NNCs

Influenza type	Age group	Outcome	NNC	Relative effect measure (95% CI)	Statistical significance (p-value)	Reference
Pandemic influenza A(H1N1)pdm09	Children	ICU admission among hospitalizations	Neurodevelopmental condition	NR	0.034	(40)
			Neurologic condition	NR	<0.001	(37)
				aOR: 7.82 (1.15–53.34)	<0.05	(41)
				aOR: 2.30 (1.14–4.61)	0.02	(71)
				aRR: 13.65 (6.48–28.77) (univariate) NR (multivariate)	<0.001 NS (multivariate)	(119)
				RR: 2.9 (1.3–6.6)	0.02	(136)
				aOR: 1.93 (1.05–3.55) (adjusted for ethnic origin)	0.04	(144)
			Neurologic or neuromuscular condition	aOR: 4.2 (1.5–11.3)	0.006	(46)
		ICU admission or death among hospitalizations	Cerebral palsy or developmental delay	aOR: 3.5 (1.7–7.4)	<0.05	(88)
			Neurologic condition	OR: 2.8 (1.6–5.0) (univariate) NR (multivariate)	<0.05 (univariate) NS (multivariate)	(88)
			Seizure disorder	NR (multivariate)	NS	(88)
		ICU admission or death among ED presentations	Cerebral palsy or developmental delay	aOR: 10.2 (2.0–51.4) (random controls) aOR: 65.9 (8.6–506) (age-matched controls)	<0.05 (random controls) <0.05 (age-matched controls)	(42)

Influenza type	Age group	Outcome	NNC	Relative effect measure (95% CI)	Statistical significance (p-value)	Reference
			Neurologic condition	NR	0.47	(33)
	Adults	ICU admission among medically-attended	Neurologic condition	aOR: 19.11 (3.92–93.22)	<0.001	(114)
		ICU admission or death among hospitalizations	Neurocognitive condition	NR	0.02	(19)
			Neuromuscular condition	NR (multivariate)	NS (multivariate)	(127)
			Seizure disorder	NR (multivariate)	NS (multivariate)	(127)
	Mixture*	ICU admission or death among hospitalizations	Cerebrovascular disease	aOR: 1.69 (0.45–6.36)	0.4350	(139)
			Epilepsy	aOR: 6.22 (2.29–16.90)	0.0003	(139)
			Neurologic condition	NR	<0.05	(68)
			Neuromuscular condition	aOR: 0.9 (0.2–3.6)	NS	(58)
				aOR: 17.81 (4.97–63.85)	<0.0001	(139)
		ICU admission, pneumonia development and/or death among medically-attended	Neuromuscular condition	NR	NS	(65)
Seasonal influenza	Children	ICU admission among hospitalizations	Neurologic condition	aRR: 6.07 (2.39–15.43)	<0.001	(119)
				aOR: 1.87 (0.25–14.14) (adjusted for ethnic origin)	0.55	(144)
			Neuromuscular condition	aOR: 4.41 (0.62–13.36)	0.14	(90)
			NNC with vaccine indications	NR	NS	(6)
			NNC without vaccine indications	OR: 1.96 (1.18–3.27)	0.02	(6)
		ICU admission among hospitalizations (infants <12 months of age)	Neurologic or neuromuscular condition	aOR: 2.99 (1.87–4.78)	<0.001	(32)
		ICU admission or death among hospitalizations	Neuromuscular condition	aOR: 4.84 (2.02–11.56)	0.0004	(31)
	Adults	ICU admission or death among hospitalizations	Neuromuscular condition	aOR: 1.68 (1.11–2.52)	0.01	(31)

Abbreviations: aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; ED, emergency department; ICU, intensive care unit; OR, odds ratio; NNC, neurologic or neurodevelopment condition; NR, not reported; NS, not significant; RR, relative risk.

* Defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for “predominantly children” or “predominantly adults”).

III.4.3 Death

Twelve studies investigated the association between NNCs and influenza-related death (Table 12)[11, 18, 22, 37, 50, 70, 85, 92, 106, 112, 118, 141]. NNCs were not identified as statistically significant risk factors for laboratory-confirmed influenza-related death in a majority of studies of mortality among influenza-related ICU admissions[11, 50, 70, 92, 118] and reported with mixed statistical significance in studies of mortality among influenza-related hospitalizations[18, 22, 37, 85, 141]. However, reported point estimates of the associations were suggestive of increased risk of death in children and all ages (i.e., "mixture of children and adults") with NNCs compared to children or persons without the NNC or any risk factors for influenza-related complications among those hospitalized or admitted to ICU with laboratory-confirmed pandemic or seasonal influenza infection. Higher effect sizes were observed for risk of death among influenza-related hospitalizations compared to risk of death among influenza-related ICU admissions (no point estimates of effect size were reported for adults).

Neurologic conditions were identified as a statistically significant risk factor for death among influenza-related hospitalizations in children[22, 37, 85] and with mixed statistical significance in studies with a mixture of children and adults[18, 141]. With the exception of one study on neurologic conditions[118], several studies did not find neurologic, neurodevelopmental or neuromuscular conditions to be statistically significant risk factors for death among influenza-related ICU admissions in children[11, 50, 70] and adults[92]. A population case series found a statistically significantly higher risk of death in adults with cerebrovascular disease or neurologic disease compared to healthy individuals[112]. This finding was similarly observed in another population case series where individuals (predominantly adults) with pre-existing neurologic disease and stroke or TIA had statistically significantly ($p<0.001$) higher age-standardized mortality rates (450 and 4.3 deaths per million, respectively) compared to individuals with no risk factors (2.4 deaths per million)[106].

Table 12: Risk of laboratory-confirmed influenza-related death in individuals with NNCs

Influenza type	Age group	Outcome	NNC	Relative effect measure (95% CI)	Statistical significance (p-value)	Reference
Pandemic influenza A(H1N1)pdm09	Children	Death among hospitalizations	Neurologic condition	NR	0.034	(37)
				OR: 5.62 (1.13–22.63)	0.003	(85)
				NR (vs. no high-risk conditions)	<0.01	(22)
		Death among ICU admissions	Neurodevelopmental condition	OR: 2.0 (0.4–13.1)	0.501	(11)
			Neurologic condition	NR	0.466	(70)
				RR: 1.8 (1.1–2.7)	0.01	(118)
	Adults	Death among ICU admissions	Neuromuscular condition	NR	0.69	(92)
		Death	Neurologic condition	aRR: 115.3 (84.3–157.6) (vs. no risk factor and no infection)	<0.05	(112)

Influenza type	Age group	Outcome	NNC	Relative effect measure (95% CI)	Statistical significance (p-value)	Reference
			Stroke or TIA	aRR: 7.5 (2.3–23.7) (vs. no risk factor and no infection)	<0.05	(112)
	Mixture*	Death among hospitalizations	Neurologic condition	aOR: 7.5 (1.5–36.4)	0.013	(18)
				OR: 2.0 (0.8–4.7)	NS	(141)
Seasonal influenza	Children	Death among ICU admissions	Neuromuscular condition	NR	0.21	(50)
	Adults	Death among ICU admissions	Neuromuscular condition	NR	0.38	(92)

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; NNC, neurologic or neurodevelopment condition; NR, not reported; NS, not significant; RR, relative risk; TIA, transient ischemic attack.
* Defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").

III.4.4 Respiratory Failure or Need for Mechanical Ventilation

Eight studies reported on the association between NNCs and respiratory failure or need for mechanical ventilation among laboratory-confirmed influenza-related hospitalizations[6, 13, 34, 37, 38, 49, 73, 141] or ICU admissions[73] (Table 13). The statistical significance of these associations was mixed, but the reported point estimates of the relative effect measures may indicate an overall increased risk of respiratory failure or need for mechanical ventilation across studies in children and adults with NNCs compared to children or adults without the NNC among those hospitalized or admitted to ICU with pandemic or seasonal influenza infection.

Table 13: Risk of laboratory-confirmed influenza-related respiratory failure or need for mechanical ventilation in individuals with NNCs

Influenza type	Age group	Outcome	NNC	Relative effect measure (95% CI)	Statistical significance (p-value)	Reference
Pandemic influenza A(H1N1)pdm09	Children	Mechanical ventilation among hospitalizations	Neurologic condition	NR	<0.001	(37)
		Mechanical ventilation among ICU admissions	Neurologic condition	aHR: 3.07 (0.52–18.18)	NS	(73)
	Mixture*	Mechanical ventilation among hospitalizations	Neurologic condition	aOR: 1.5 (0.7–3.2) (with obesity as covariate)	NS	(141)

Influenza type	Age group	Outcome	NNC	Relative effect measure (95% CI)	Statistical significance (p-value)	Reference
		Respiratory failure and pneumonia among hospitalizations	Neurodevelopmental condition	NR	NS	(34)
Seasonal influenza	Children	Respiratory failure among hospitalizations	Neurologic or neuromuscular condition	aOR: 6.0 (2.7–13.5)	<0.05	(38)
		Mechanical ventilation among hospitalizations	Neurologic condition	aOR: 4.05 (3.79–4.33)	<0.001	(49)
			NNC with vaccine indications	NR	NS	(6)
			NNC without vaccine indications	OR: 3.70 (1.95–7.01)	<0.001	(6)
	Adults	Respiratory failure or death among hospitalizations	Stroke or TIA	OR: 3.0 (univariate) NR (multivariate)	0.01 (univariate) 0.018 (multivariate)	(13)

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; NNC, neurologic or neurodevelopment condition; OR, odds ratio; NR, not reported; NS, not significant; TIA, transient ischemic attack.

* Defined as a study population with greater than 30%, but less than 70% of either children or adults (i.e., study population does not meet the review definition for "predominantly children" or "predominantly adults").

III.5 Exacerbation of Pre-Existing NNCs Following Laboratory-Confirmed Influenza Virus Infection

Four studies included for review investigated the exacerbation of pre-existing NNCs following laboratory-confirmed influenza virus infection. Dementia was found to be the second most commonly exacerbated pre-existing disease, after chronic respiratory disease, among adults presenting to EDs with seasonal influenza A infection[100]. In children, one study did not find an association between previous history of seizures and seizure as a neurologic complication of pandemic influenza infection among hospitalized cases (p=0.21)[76]; however, another study found that 16 of 17 (94.1%) cases with pre-existing seizures experienced post-infection breakthrough seizures or exacerbation of seizures[104]. In a small subgroup analysis, two of two (100.0%) adults with pre-existing MG experienced exacerbation of their underlying condition[116].

III.6 Prevention of Influenza Infection in Individuals with NNCs Following Influenza Vaccination

No studies included for review assessed the potential prevention of influenza infection or amelioration of its complications in individuals with pre-existing NNCs following influenza vaccination.

III.7 Influenza Vaccination Impact on Pre-Existing NNCs Following Influenza Infection

A small number of vaccine safety studies were identified in the present review that investigated the impact of influenza vaccination on specific, pre-existing NNCs: epilepsy[14], multiple sclerosis (MS)[45, 94, 95, 99, 105, 133], MG[15, 152], stroke and TIA[80, 135]. However, these studies did not assess for influenza infection and so could not directly assess the impact of vaccination on disease course after subsequent influenza infection. In the absence of direct evidence for this review objective, these studies at least provide some evidence that influenza vaccination on its own does not appear to directly influence the course of specific, pre-existing NNCs.

A self-controlled case series found no increased risk of seizures in individuals with previously diagnosed epilepsy who were vaccinated with monovalent AS03-adjuvanted pandemic influenza A(H1N1)pdm09 vaccine during risk periods (1–7 and 8–30 days post-vaccination) compared to control periods (90–30 pre-vaccination and 31–90 days post-vaccination) (relative incidence: 1.00 to 1.01)[14].

Three double-blind, placebo-controlled trials found that seasonal influenza vaccination was neither associated with an increased exacerbation rate of MS[95, 99, 105] nor a change in disease course of MS[95] following vaccination. Of these trials, one reported that the mean time to onset of MS relapse after vaccination was longer for influenza vaccine recipients (mean: 91.5 days, standard deviation [SD]: 61.9 days) compared to placebo recipients (mean: 55.3 days, SD: 36.4 days), but this difference was not statistically significant. An uncontrolled before-after trial also reported a lack of clinical exacerbation of MS following seasonal influenza vaccination (RR: 0.45, 95% CI: 0.035–5.843)[94]. In a clinical case series, the observed relapse rate in MS patients vaccinated with seasonal influenza vaccine (0.6 attacks per patient per year) was less than the expected rate in the natural course of MS illness[133]. Finally, a self-controlled case series that conducted subgroup analysis by type of MS found that no MS patients with primary progressive MS reported clinically relevant exacerbations within six weeks following seasonal influenza vaccination while 5.0% of MS patients with relapsing MS experienced exacerbation after seasonal influenza vaccination[45]. A statistically significantly higher proportion of MS patients with relapsing MS experienced exacerbations within six weeks of influenza illness compared to influenza vaccination (33.3% vs. 5.0%, $p<0.0001$)[45].

A clinical case series reported no myasthenic exacerbation in MG patients (n=74) following pandemic and/or seasonal influenza vaccination after at least eight weeks of follow up[15]. Similarly, a self-controlled case series found no increased risk of hospitalization for exacerbation of MG following seasonal influenza vaccination during the risk interval (0–6 weeks post-vaccination) compared to the control interval (18–42 weeks post-vaccination) (relative incidence: 0.84, 95% CI: 0.65–1.09)[152].

A case-cohort study using pooled data from two prospective cohort studies and one randomized controlled trial found no association between seasonal influenza vaccination and risk of recurrent stroke or TIA (propensity score-matched hazard ratio [HR]: 1.01, 95% CI: 0.88–1.17, p=0.89), stroke alone (matched HR: 1.01, 95% CI: 0.86–1.18) or TIA alone (matched HR: 1.33, 95% CI: 0.30–5.96)[80]. However, a self-controlled case series found that the incidence rate of recurrent stroke was statistically significantly lower in post-vaccination risk periods (1–91 days post-vaccination) compared to baseline periods (age-adjusted incidence ratio: 0.56 to 0.79)[135].

IV. DISCUSSION

The majority of identified studies in the present rapid literature review were descriptive studies (i.e., case series) that examined the clinical characteristics, including risk factors for influenza complications, of patients that presented with serious influenza-related complications and who had laboratory-confirmed pandemic influenza A(H1N1)pdm09 or seasonal influenza infection. While studies included for review were generally heterogeneous in design and parameters, the body of evidence appears to suggest a relatively high burden of pre-existing NNCs in children and adults who had experienced serious pandemic and seasonal influenza-related hospitalizations, ICU admissions and deaths. Higher proportions of NNCs were seen for pediatric influenza-related outcomes compared to adults. A trend of increasing prevalence of NNCs with increasing severity of influenza-related complications (e.g., hospitalization < ICU admission < death) was observed. Prevalence data were more limited for ED presentation, respiratory failure and need for mechanical ventilation and ranged widely in reported values. There was limited, but consistent evidence to suggest that pre-existing NNCs increased the risk for these serious influenza-related complications. No association studies were identified that examined NNCs as a risk factor for influenza-related ED presentation. There is a relative preponderance of identified evidence as well as a stronger body of evidence for children compared to adults and for pandemic influenza compared to seasonal influenza with respect to pre-existing NNCs as a factor associated with serious influenza-related complications. These findings should be interpreted in consideration of the lower quality evidence comprising the bulk of identified evidence (i.e., the case series design [level III evidence] is more vulnerable to confounding and bias and is limited in its conclusions compared to controlled trials [levels I and II-1 evidence] or observational analytic designs [level II-2 evidence], such as case-control, which is vulnerable to the fact that cases and controls are not arising from the same population, or cohort studies) as well as a lack of clarity in the composition of conditions constituting NNCs in some studies and a lack of consistency across identified studies in the defined lists of specific NNCs investigated.

Only four studies were identified that examined the exacerbation of laboratory-confirmed influenza infection on disease course or complications related to pre-existing NNCs. Dementia was found to be among the more commonly influenza-exacerbated chronic diseases in adults[100]. One study of adults found suggestive evidence based on a small subgroup analysis of only two cases that MG was exacerbated following influenza infection[116]. However, there was mixed evidence of exacerbation of pre-existing seizure disorders in children following influenza infection[76, 104]. There was no identified evidence assessing whether or not influenza vaccination could prevent influenza infection and its complications in individuals with pre-existing NNCs. No direct evidence was found assessing whether or not influenza vaccination could worsen or attenuate a worsening of pre-existing NNCs after subsequent influenza infection, because the small number of vaccine safety studies identified did not assess for influenza infection subsequent to vaccination. However, these studies did provide some evidence that influenza vaccination on its own does not appear to directly influence the course of specific, pre-existing NNCs.

Several limitations at the review level as well as at the individual study level should be additionally considered when interpreting the body of evidence synthesized in the present literature review. In particular, findings of the present rapid literature review should be interpreted with caution in light of the potential for biases as a consequence of concessions made to the systematic review process due to time and resource constraints.

Despite efforts to conduct a rigorous and comprehensive synthesis of available evidence on NNCs and serious influenza-related complications, the totality of evidence on this topic was not captured in the present literature review, as evidenced by the number of additional studies identified by handsearching. A possible explanation for the large number of relevant studies identified by handsearching may be due to the breadth of descriptive studies (i.e., case series) in the body of evidence that conducted exploratory analysis for study-defined risk factors of influenza-related complications whereas a limited number of studies specifically investigated NNCs as a risk factor. Database searching within the title and abstract fields may not have been able to capture the exploratory studies that did not specify terms for NNCs in these indexed database fields. Of the 26 studies identified from handsearching a 10% random subset of eligible studies identified from the database searches, 25 were case series. Therefore, due to time and resource constraints for the present review, handsearching for this particular topic may be of limited added value in identifying studies with designs more robust than case series. Additionally, single reviewer screening for eligible studies may have resulted in study misclassification during the study selection process, where potentially eligible studies may have been inadvertently screened out.

Publication bias is an important limitation of any review and may skew the balance of findings to positive findings[160]. Quantitative assessment for publication bias was not performed for the present literature review. Furthermore, the scope of the present review was restricted to the stated review objectives; as such, this review did not examine interaction risks between NNCs and comorbid chronic health conditions that may confer high risk of influenza-related complications, including cardiac or pulmonary disorders, diabetes mellitus, immune compromising conditions and other high-risk conditions as identified in the Statement[4].

At the individual study level, the descriptive nature of the majority of identified studies (i.e., case series) addressing the present review's primary outcomes of interest is a major limitation of the body of evidence. The case series design is considered of lower quality (level III evidence) as it is more vulnerable to confounding and bias and is limited in its conclusions compared to controlled trials (level I and II-1 evidence) and observational analytic designs (level II-2 evidence). There was also a lack of clarity in the composition of conditions constituting NNCs in some studies and a lack of consistency across identified studies in the defined lists of specific NNCs investigated. The present review attempted to group these heterogeneously defined NNCs as well as outcomes by similarity of definition for qualitative synthesis, with a loss of individual study-level granularity. It should be noted that there were also differences across studies in populations, case definitions and epidemiological characteristics that may be masked with the pooling of findings. In addition, besides the pediatric IMPACT study, which found a notable burden of severe influenza in children with isolated seizure disorders or isolated developmental delay[6], investigation of isolated NNCs (e.g., with NNC, but without other high-risk conditions) as risk factors for influenza-related complications was not clearly established in the included studies. Furthermore, there is a paucity of identified studies comparing the relative risk of laboratory-confirmed influenza-related complications in individuals with NNCs to healthy individuals, rather than individuals without NNCs, but may have other high-risk chronic health conditions; this limitation may be attributed to individual study design and analysis needs that are not of direct relevance to the present review's objectives.

Overall, the body of evidence identified in the present rapid literature review is suggestive of a relatively high burden of pre-existing NNCs in children and adults who experienced serious pandemic influenza A(H1N1)pdm09- and seasonal influenza-related complications, such as hospitalization, ICU admission and death. There is also consistent evidence to suggest that pre-existing NNCs increase the risk for these serious influenza-related complications. Both of these

observed trends are consistent with the preliminary evidence supporting children and adults with NNCs as groups at risk for influenza-related complications and hospitalization[4]. Aside from the IMPACT case series in children[6], there was no other study identified that specifically investigated NNCs in relation to burden or risk of serious influenza-related complications by respiratory compromise status. Therefore, it is not known if the IMPACT study finding, suggesting that respiratory compromise is not a necessary condition of NNCs to increase risk for serious influenza-related complications in children, could be replicated in children and extrapolated to adults. There is also a need for further investigation into the impact of influenza infection on the course of pre-existing NNCs and whether influenza vaccination of individuals with pre-existing NNCs prevents influenza and its complications in this population or worsens or attenuates a worsening of their condition after subsequent influenza infection.

V. LIST OF ABBREVIATIONS

Abbreviation	Term
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
aHR	Adjusted hazard ratio
AIH	Australian Immunisation Handbook
aOR	Adjusted odds ratio
ARDS	Acute respiratory distress syndrome
ARI	Acute respiratory illness
aRR	Adjusted relative risk
CFR	Case fatality ratio
CI	Confidence interval
CNS	Central nervous system
DFA	Direct fluorescent antibody
DH	Department of Health
ED	Emergency department
HR	Hazard ratio
ICD	International Classification of Diseases
ICU	Intensive care unit
ILI	Influenza-like illness
IQR	Interquartile range
IR	Incidence ratio
MG	Myasthenia gravis
MS	Multiple sclerosis
n/a	Not applicable
NA	Not available
NACI	National Advisory Committee on Immunization
NNC	Neurologic or neurodevelopment condition
NR	Not reported
NS	Not significant
OR	Odds ratio
p	p-value
PAF	Population attributable fraction
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
RIDT	Rapid influenza diagnostic test
RR	Relative risk
RT-PCR	Reverse transcriptase polymerase chain reaction
rtRT-PCR	Real-time reverse transcriptase polymerase chain reaction
SARI	Severe acute respiratory illness

SD	Standard deviation
SMR	Standardized mortality rate
TIA	Transient ischemic attack
UK	United Kingdom
USA	United States of America
WHO-ATC	World Health Organization Anatomical Therapeutic Chemical

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VII. REFERENCES

1. Public Health Agency of Canada (PHAC). Mapping connections: an understanding of neurological conditions in Canada [Internet]. 2014. Available from: http://www.phac-aspc.gc.ca/publicat/cd-mc/mc-ec/introduction-eng.php.

2. World Health Organization (WHO). Neurological disorders: public health challenges [Internet]. 2006. Available from: http://www.who.int/mental_health/neurology/neurodiso/en/.

3. National Advisory Committee on Immunization (NACI). Evidence-based recommendations for immunization - methods of the National Advisory Committee on Immunization. Can Commun Dis Rep. 2009;35(ACS-1):1-10.

4. National Advisory Committee on Immunization (NACI). Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016-2017 [Internet]. 2016. Available from: http://www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-eng.php.

5. National Advisory Committee on Immunization (NACI). Statement on Seasonal Influenza Vaccine for 2015-2016 [Internet]. 2015. Available from: http://www.phac-aspc.gc.ca/naci-ccni/flu-2015-grippe-eng.php.

6. Burton C, Vaudry W, Moore D, et al. Burden of seasonal influenza in children with neurodevelopmental conditions. Pediatr Infect Dis J. 2014;33(7):710-4.

7. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3):21-35.

8. Ahrens JO, Morrow BM, Argent AC. Influenza A(H1N1)pdm09 in critically ill children admitted to a paediatric intensive care unit, South Africa. Southern African Journal of Critical Care. 2015;31(1):4-7.

9. Al Soub H, Ibrahim AS, Al Maslamani M, Al-khal AL, Shaath S, Hamza NA. Epidemiology, risk factors, clinical features, and outcome of adult patients with severe pandemic A/H1N1/2009 influenza in Qatar: a retrospective study. Infectious Diseases in Clinical Practice. 2014;22(6):339-43.

10. Al Subaie SS, Al Saadi MA. Features associated with severe disease in hospitalized children with 2009 influenza A (H1N1) infection at a university hospital in Riyadh, Saudi Arabia. Ann Saudi Med. 2012;32(1):53-8.

11. Altmann M, Fiebig L, Soyka J, von Kries R, Dehnert M, Haas W. Severe cases of pandemic (H1N1) 2009 in children, Germany. Emerg Infect Dis. 2011;17(2):186-92.

12. Ampofo K, Gesteland PH, Bender J, et al. Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection. Pediatrics. 2006;118(6):2409-17.

13. Angelo SJ, Marshall PS, Chrissoheris MP, Chaves AM. Clinical characteristics associated with poor outcome in patients acutely infected with Influenza A. Conn Med. 2004;68(4):199-205.

14. Arnheim-Dahlstrom L, Hallgren J, Weibull CE, Sparen P. Risk of presentation to hospital with epileptic seizures after vaccination with monovalent AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix): self controlled case series study. BMJ. 2012;345:e7594.

15. Auriel E, Regev K, Dori A, Karni A. Safety of influenza and H1N1 vaccinations in patients with myasthenia gravis, and patient compliance. Muscle Nerve. 2011;43(6):893-4.

16. Bagdure D, Curtis DJ, Dobyns E, Glode MP, Dominguez SR. Hospitalized children with 2009 pandemic influenza A (H1N1): comparison to seasonal influenza and risk factors for admission to the ICU. PLoS ONE. 2010;5(12):e15173.

17. Balanzat AM, Hertlein C, Apezteguia C, et al. An analysis of 332 fatalities infected with pandemic 2009 influenza A (H1N1) in Argentina. PLoS ONE. 2012;7(4):e33670.

18. Barakat A, Ihazmad H, El Falaki F, Tempia S, Cherkaoui I, El Aouad R. 2009 Pandemic influenza A virus subtype H1N1 in Morocco, 2009-2010: epidemiology, transmissibility, and factors associated with fatal cases. J Infect Dis. 2012;206(Suppl 1):S94-100.

19. Bassetti M, Parisini A, Calzi A, et al. Risk factors for severe complications of the novel influenza A (H1N1): analysis of patients hospitalized in Italy. Clin Microbiol Infect. 2011;17(2):247-50.

20. Bennet R, Hamrin J, Wirgart BZ, Östlund MR, Örtqvist Å, Eriksson M. Influenza epidemiology among hospitalized children in Stockholm, Sweden 1998–2014. Vaccine. 2016;34(28):3298-302.

21. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003-2004. N Engl J Med. 2005;353(24):2559-67.

22. Blanton L, Peacock G, Cox C, Jhung M, Finelli L, Moore C. Neurologic disorders among pediatric deaths associated with the 2009 pandemic influenza. Pediatrics. 2012;130(3):390-6.

23. Blumental S, Huisman E, Cornet M, et al. Pandemic A/H1N1v influenza 2009 in hospitalized children: a multicenter Belgian survey. BMC Infect Dis. 2011;11:313.

24. Brink M, Hagberg L, Larsson A, Gedeborg R. Respiratory support during the influenza A (H1N1) pandemic flu in Sweden. Acta Anaesthesiol Scand. 2012;56(8):976-86.

25. Brocklebank JT, Court SD, McQuillin J, Gardner PS. Influenza-A infection in children. Lancet. 1972;2(7776):497-500.

26. Calitri C, Gabiano C, Garazzino S, et al. Clinical features of hospitalised children with 2009 H1N1 influenza virus infection. Eur J Pediatr. 2010;169(12):1511-5.

27. Campbell CNJ, Mytton OT, McLean EM, et al. Hospitalization in two waves of pandemic influenza A(H1N1) in England. Epidemiol Infect. 2011;139(10):1560-9.

28. Cardenosa N, Rodes A, Follia N, et al. Epidemiological analysis of severe hospitalized 2009 pandemic influenza A (H1N1) cases in Catalonia, Spain. Hum Vaccin. 2011;7(Suppl):226-9.

29. Centers for Disease Control and Prevention (CDC). Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection - United States, April-August 2009. MMWR Morb Mortal Wkly Rep. 2009;58(34):941-7.

30. Chacon R, Mirza S, Rodriguez D, et al. Demographic and clinical characteristics of deaths associated with influenza A(H1N1) pdm09 in Central America and Dominican Republic 2009-2010. BMC Public Health. 2015;15:734.

31. Chaves SS, Aragon D, Bennett N, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010-2011 influenza season: exploring disease severity by virus type and subtype. J Infect Dis. 2013;208(8):1305-14.

32. Chaves SS, Perez A, Farley MM, et al. The burden of influenza hospitalizations in infants from 2003 to 2012, United States. Pediatr Infect Dis J. 2014;33(9):912-9.

33. Chen W, Lu C, Shao P, et al. Risk factors of severe novel influenza A (H1N1) infections in hospitalized children. J Formosan Med Assoc. 2012;111(8):421-6.

34. Chien Y, Su C, Tsai H, et al. Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan. J Infect. 2010;60(2):168-74.

35. Chiu SS, Chan K, Wong WHS, Chan ELY, Peiris JSM. Age-matched comparison of children hospitalized for 2009 pandemic H1N1 influenza with those hospitalized for seasonal H1N1 and H3N2. PLoS ONE. 2011;6(7):e21837.

36. Chong CY, Tan NW, Menon A, Thoon KC, Tee NWS, Fu S. Risk factors for complicated influenza A (H1N1) 2009 disease in children. Ann Acad Med Singapore. 2013;42(5):232-6.

37. Ciftci E, Tuygun N, Ozdemir H, et al. Clinical and epidemiological features of Turkish children with 2009 pandemic influenza A (H1N1) infection: experience from multiple tertiary paediatric centres in Turkey. Scand J Infect Dis. 2011;43(11-12):923-9.

38. Coffin SE, Zaoutis TE, Rosenquist ABW, et al. Incidence, complications, and risk factors for prolonged stay in children hospitalized with community-acquired influenza. Pediatrics. 2007;119(4):740-8.

39. Cox CM, Blanton L, Dhara R, Brammer L, Finelli L. 2009 Pandemic influenza A (H1N1) deaths among children--United States, 2009-2010. Clin Infect Dis. 2011;52(Suppl 1):S69-74.

40. Custodio HT, Gayle MO, Bailey CS, Wludyka PS, Rathore MH. Comparison of ICU and non-ICU patients infected with the 2009 H1N1 influenza virus in a Florida Children's hospital between April and December 2009. Eastern Journal of Medicine. 2011;16(3):188.

41. Da Dalt L, Chillemi C, Cavicchiolo ME, et al. Pandemic influenza A (H1N1v) infection in pediatric population: a multicenter study in a north-east area of Italy. Ital J Pediatr. 2011;37:24.

42. Dalziel SR, Thompson JM, Macias CG, et al. Predictors of severe H1N1 infection in children presenting within Pediatric Emergency Research Networks (PERN): retrospective case-control study. BMJ. 2013;347:f4836.

43. Damak H, Chtara K, Bahloul M, et al. Clinical features, complications and mortality in critically ill patients with 2009 influenza A(H1N1) in Sfax, Tunisia. Influenza Other Respir Viruses. 2011;5(4):230-40.

44. Dawood FS, Fiore A, Kamimoto L, et al. Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008. J Pediatr. 2010;157(5):808-14.

45. De Keyser J, Zwanikken C, Boon M. Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. J Neurol Sci. 1998;159(1):51-3.

46. del Rosal T, Baquero-Artigao F, Calvo C, et al. Pandemic H1N1 influenza-associated hospitalizations in children in Madrid, Spain. Influenza Other Respir Viruses. 2011;5(6):e544-51.

47. Desmoulins C, Michard-Lenoir A, Naud J, Claudet I, Nouyrigat V, Cheron G. [Clinical features and outcome of 2009 H1N1 influenza in the pediatric setting. Multicenter prospective study in the ED]. Arch Pediatr. 2011;18(5):505-11.

48. Dhanoa A, Fang NC, Hassan SS, Kaniappan P, Rajasekaram G. Epidemiology and clinical characteristics of hospitalized patients with pandemic influenza A (H1N1) 2009 infections: the effects of bacterial coinfection. Virol J. 2011;8:501.

49. Eriksson CO, Graham DA, Uyeki TM, Randolph AG. Risk factors for mechanical ventilation in U.S. children hospitalized with seasonal influenza and 2009 pandemic influenza A*. Pediatr Crit Care Med. 2012;13(6):625-31.

50. Farias JA, Fernández A, Monteverde E, et al. Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina. Intensive Care Med. 2010;36(6):1015-22.

51. Ferdinands JM, Olsho LE, Agan AA, et al. Effectiveness of influenza vaccine against life-threatening RT-PCR-confirmed influenza illness in US children, 2010-2012. J Infect Dis. 2014;210(5):674-83.

52. Feret V, Naud J, Harambat J, Malato L, Fleury H, Fayon M. [Viral epidemiology and clinical severity during the peak of the influenza A(H1N1) variant epidemic in febrile respiratory diseases of children]. Arch Pediatr. 2014;21(7):709-15.

53. Fowlkes AL, Arguin P, Biggerstaff MS, et al. Epidemiology of 2009 pandemic influenza A (H1N1) deaths in the United States, April-July 2009. Clin Infect Dis. 2011;52(Suppl 1):S60-8.

54. Garcia MN, Philpott DC, Murray KO, et al. Clinical predictors of disease severity during the 2009-2010 A(HIN1) influenza virus pandemic in a paediatric population. Epidemiol Infect. 2015;143(14):2939-49.

55. Garnacho-Montero J, Gutierrez-Pizarraya A, Marquez JA, et al. Epidemiology, clinical features, and prognosis of elderly adults with severe forms of influenza A (H1N1). J Am Geriatr Soc. 2013;61(3):350-6.

56. Gastanaduy AS, Begue RE. Experience with pandemic 2009 H1N1 influenza in a large pediatric hospital. South Med J. 2012;105(4):192-8.

57. Gauzere B, Bussienne F, Bouchet B, et al. [Severe cases of A(H1N1)v2009 infection in Reunion Island in 2009 and 2010]. Bull Soc Pathol Exot. 2011;104(2):97-104.

58. Gilca R, De Serres G, Boulianne N, et al. Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. Influenza Other Respir Viruses. 2011;5(4):247-55.

59. Godoy P, Castilla J, Mayoral JM, et al. Smoking may increase the risk of hospitalization due to influenza. Eur J Public Health. 2016;26(5):882-7.

60. Gonzalez-Candelas F, Astray J, Alonso J, et al. Sociodemographic factors and clinical conditions associated to hospitalization in influenza A (H1N1) 2009 virus infected patients in Spain, 2009-2010. PLoS ONE. 2012;7(3):e33139.

61. Grgic S, Skocibusic S, Celjuska-Tosev E, Nikolic J, Arapovic J, Kuzman I. Different features of influenza A H1N1pdm09 virus infection among adults in 2009/10 and 2010/11. J Infect Dev Ctries. 2016;10(2):155-62.

62. Gubbels S, Krause TG, Bragstad K, Perner A, Mølbak K, Glismann S. Burden and characteristics of influenza A and B in Danish intensive care units during the 2009/10 and 2010/11 influenza seasons. Epidemiol Infect. 2013;141(04):767-75.

63. Hagerman A, Posfay-Barbe KM, Duppenthaler A, Heininger U, Berger C, PIGS Influenza Study Group. Clinical characteristics and outcomes in children hospitalised with pandemic influenza A/H1N1/09 virus infection - a nationwide survey by the Pediatric Infectious Diseases Group of Switzerland. Swiss Med Wkly. 2015;145:w14171.

64. Heininger U, Baer G, Ryser A, Li Y. Comparative analysis of clinical characteristics of pandemic influenza a/h1n1 and seasonal influenza A infections in hospitalized children. Pediatr Infect Dis J. 2013;32(3):293-6.

65. Hlavinkova L, Kristufkova Z, Mikas J. Risk factors for severe outcome of cases with pandemic influenza A(H1N1)pdm09. Bratisl Lek Listy. 2015;116(6):389-93.

66. Hon KL, Leung E, Hung E, et al. Premorbid factors and outcome associated with respiratory virus infections in a pediatric intensive care unit. Pediatr Pulmonol. 2008;43(3):275-80.

67. Hong K, Cheong HJ, Choi WS, et al. Clinical courses and outcomes of hospitalized adult patients with seasonal influenza in Korea, 2011-2012: Hospital-based Influenza Morbidity & Mortality (HIMM) surveillance. J Infect Chemother. 2014;20(1):9-14.

68. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med. 2009;361(20):1935-44.

69. Kappagoda C, Isaacs D, Mellis C, Peat J, De Silva L, O'Connell A. Critical influenza virus infection. J Paediatr Child Health. 2000;36(4):318-21.

70. Kendirli T, Demirkol D, Yildizdas D, et al. Critically ill children with pandemic influenza (H1N1) in pediatric intensive care units in Turkey. Pediatr Crit Care Med. 2012;13(1):e11-7.

71. Khandaker G, Zurynski Y, Ridley G, et al. Clinical epidemiology and predictors of outcome in children hospitalised with influenza A(H1N1)pdm09 in 2009: a prospective national study. Influenza Other Respir Viruses. 2014;8(6):636-45.

72. Koh MT, Eg KP, Loh SS. Hospitalised Malaysian children with pandemic (H1N1) 2009 influenza: clinical characteristics, risk factors for severe disease and comparison with the 2002-2007 seasonal influenza. Singapore Med J. 2016;57(2):81-6.

73. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA. 2009;302(17):1872-9.

74. Kumar S, Havens PL, Chusid MJ, Willoughby REJ, Simpson P, Henrickson KJ. Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. Pediatr Infect Dis J. 2010;29(7):591-4.

75. Kwong KL, Lung D, Wong SN, Que TL, Kwong NS. Influenza-related hospitalisations in children. J Paediatr Child Health. 2009;45(11):660-4.

76. Landau YE, Grisaru-Soen G, Reif S, Fattal-Valevski A. Pediatric neurologic complications associated with influenza A H1N1. Pediatr Neurol. 2011;44(1):47-51.

77. Larcombe PJ, Moloney SE, Schmidt PA. Pandemic (H1N1) 2009: a clinical spectrum in the general paediatric population. Arch Dis Child. 2011;96(1):96-8.

78. Launes C, Garcia-Garcia JJ, Martinez-Planas A, et al. Clinical features of influenza disease in admitted children during the first postpandemic season and risk factors for hospitalization: a multicentre Spanish experience. Clin Microbiol Infect. 2013;19(3):E157-62.

79. Launes C, Garcia-Garcia J, Martinez-Planas A, et al. 2009 H1N1: risk factors for hospitalization in a matched case-control study. Eur J Pediatr. 2012;171(7):1127-31.

80. Lavallee PC, Labreuche J, Fox KM, et al. Influenza vaccination and cardiovascular risk in patients with recent TIA and stroke. Neurology. 2014;82(21):1905-13.

81. Lee E, Seo J, Kim H, et al. Clinical characteristics and outcomes among pediatric patients hospitalized with pandemic influenza A/H1N1 2009 infection. Korean J Pediatr. 2011;54(8):329-34.

82. Lee MC, Kim HY, Kong SG, et al. Clinical characteristics of pandemic influenza A (H1N1) 2009 pediatric infection in Busan and Gyeongsangnam-do: one institution. Tuberc Respir Dis (Seoul). 2012;72(6):493-500.

83. Lees EA, Carrol ED, Gerrard C, et al. Characterisation of acute respiratory infections at a United Kingdom paediatric teaching hospital: observational study assessing the impact of influenza A (2009 pdmH1N1) on predominant viral pathogens. BMC Infect Dis. 2014;14:343.

84. Lehners N, Geis S, Eisenbach C, Neben K, Schnitzler P. Changes in severity of influenza A(H1N1)pdm09 infection from pandemic to first postpandemic season, Germany. Emerg Infect Dis. 2013;19(5):748-55.

85. Libster R, Bugna J, Coviello S, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med. 2010;362(1):45-55.

86. Liu L, Zhang R, Lu H, et al. Sixty-two severe and critical patients with 2009 influenza A (H1N1) in Shanghai, China. Chin Med J. 2011;124(11):1662-6.

87. Lockman JL, Fischer WA, Perl TM, Valsamakis A, Nichols DG. The critically ill child with novel H1N1 influenza A: a case series. Pediatr Crit Care Med. 2010;11(2):173-8.

88. Louie JK, Gavali S, Acosta M, et al. Children hospitalized with 2009 novel influenza A(H1N1) in California. Arch Pediatr Adolesc Med. 2010;164(11):1023-31.

89. Louie JK, Schechter R, Honarmand S, et al. Severe pediatric influenza in California, 2003-2005: implications for immunization recommendations. Pediatrics. 2006;117(4):e610-8.

90. Ma H, Wu J, Lu C, et al. Risk factors associated with severe influenza virus infections in hospitalized children during the 2013 to 2014 season. J Microbiol Immunol Infect. 2016;49(3):387-93.

91. Macesic N, Kotsimbos TC, Kelly P, Cheng AC. Hospital-acquired influenza in an Australian sentinel surveillance system. Med J Aust. 2013;198(7):370-2.

92. Martin-Loeches I, Diaz E, Vidaur L, et al. Pandemic and post-pandemic influenza A (H1N1) infection in critically ill patients. Crit Care. 2011;15(6):R286.

93. Meury S, Zeller S, Heininger U. Comparison of clinical characteristics of influenza and respiratory syncytial virus infection in hospitalised children and adolescents. Eur J Pediatr. 2004;163(7):359-63.

94. Michielsens B, Wilms G, Marchal G, Carton H. Serial magnetic resonance imaging studies with paramagnetic contrast medium: assessment of disease activity in patients with multiple sclerosis before and after influenza vaccination. Eur Neurol. 1990;30(5):258-9.

95. Miller AE, Morgante LA, Buchwald LY, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. Neurology. 1997;48(2):312-4.

96. Milne BG, Williams S, May MLA, Kesson AM, Gillis J, Burgess MA. Influenza A associated morbidity and mortality in a Paediatric Intensive Care Unit. Commun Dis Intell Q Rep. 2004;28(4):504-9.

97. Miroballi Y, Baird JS, Zackai S, et al. Novel influenza A(H1N1) in a pediatric health care facility in New York City during the first wave of the 2009 pandemic. Arch Pediatr Adolesc Med. 2010;164(1):24-30.

98. Mistry RD, Fischer JB, Prasad PA, Coffin SE, Alpern ER. Severe complications in influenza-like illnesses. Pediatrics. 2014;134(3):e684-90.

99. Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. Mult Scler. 1997;3(4):243-7.

100. Monmany J, Rabella N, Margall N, Domingo P, Gich I, Vazquez G. Unmasking influenza virus infection in patients attended to in the emergency department. Infection. 2004;32(2):89-97.

101. Moore DL, Vaudry W, Scheifele DW, et al. Surveillance for influenza admissions among children hospitalized in Canadian immunization monitoring program active centers, 2003-2004. Pediatrics. 2006;118(3):e610-9.

102. Morgan CI, Hobson MJ, Seger B, Rice MA, Staat MA, Wheeler DS. 2009 pandemic influenza A (H1N1) in critically ill children in Cincinnati, Ohio. Pediatr Crit Care Med. 2012;13(3):e140-4.

103. Morris SK, Parkin P, Science M, et al. A retrospective cross-sectional study of risk factors and clinical spectrum of children admitted to hospital with pandemic H1N1 influenza as compared to influenza A. BMJ Open. 2012;2(2):e000310.

104. Muhammad Ismail HI, Teh CM, Lee YL, National Paediatric H1N1 Study Group. Neurologic manifestations and complications of pandemic influenza A H1N1 in Malaysian children: what have we learnt from the ordeal? Brain Dev. 2015;37(1):120-9.

105. Myers LW, Ellison GW, Lucia M, et al. Swine influenza virus vaccination in patients with multiple sclerosis. J Infect Dis. 1977;136(Suppl):S546-54.

106. Mytton OT, Rutter PD, Mak M, Stanton EAI, Sachedina N, Donaldson LJ. Mortality due to pandemic (H1N1) 2009 influenza in England: a comparison of the first and second waves. Epidemiol Infect. 2012;140(9):1533-41.

107. Norfolk SG, Hollingsworth CL, Wolfe CR, et al. Rescue therapy in adult and pediatric patients with pH1N1 influenza infection: a tertiary center intensive care unit experience from April to October 2009. Crit Care Med. 2010;38(11):2103-7.

108. Okumura A, Nakagawa S, Kawashima H, et al. Deaths associated with pandemic (H1N1) 2009 among children, Japan, 2009-2010. Emerg Infect Dis. 2011;17(11):1993-2000.

109. Ono S, Ono Y, Matsui H, Yasunaga H. Factors associated with hospitalization for seasonal influenza in a Japanese nonelderly cohort. BMC Public Health. 2016;16:922.

110. Ostovar GA, Rubin LG, Rajan S, Sood SK, Kohn N. Comparison of the clinical features of children hospitalized with pandemic 2009 A:H1N1 and seasonal influenza. Clin Pediatr (Phila). 2011;50(4):348-54.

111. Owayed AF, Husain EH, Al-Khabaz A, Al-Qattan HY, Al-Shammari N. Epidemiology and clinical presentation of pandemic influenza A (H1N1) among hospitalized children in Kuwait. Med Princ Pract. 2012;21(3):254-8.

112. Pebody RG, McLean E, Zhao H, et al. Pandemic Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Euro Surveill. 2010;15(20).

113. Pinilla I, de Gracia MM, Quintana-Diaz M, Figueira JC. Radiological prognostic factors in patients with pandemic H1N1 (pH1N1) infection requiring hospital admission. Emerg Radiol. 2011;18(4):313-9.

114. Poeppl W, Hell M, Herkner H, et al. Clinical aspects of 2009 pandemic influenza A (H1N1) virus infection in Austria. Infection. 2011;39(4):341-52.

115. Poulakou G, Souto J, Balcells J, et al. First influenza season after the 2009 pandemic influenza: characteristics of intensive care unit admissions in adults and children in Vall d'Hebron Hospital. Clin Microbiol Infect. 2012;18(4):374-80.

116. Prerna A, Lim JYX, Tan NWH, et al. Neurology of the H1N1 pandemic in Singapore: a nationwide case series of children and adults. J Neurovirol. 2015;21(5):491-9.

117. Quach C, Piche-Walker L, Platt R, Moore D. Risk factors associated with severe influenza infections in childhood: implication for vaccine strategy. Pediatrics. 2003;112(3 Pt 1):e197-201.

118. Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics. 2011;128(6):e1450-8.

119. Rebolledo J, Igoe D, O'donnell J, et al. Influenza in hospitalized children in Ireland in the pandemic period and the 2010/2011 season: risk factors for paediatric intensive-care-unit admission. Epidemiol Infect. 2014;142(09):1826-35.

120. Reed C, Chaves SS, Perez A, et al. Complications among adults hospitalized with influenza: a comparison of seasonal influenza and the 2009 H1N1 pandemic. Clin Infect Dis. 2014;59(2):166-74.

121. Regan J, Fowlkes A, Biggerstaff M, et al. Epidemiology of influenza A (H1N1)pdm09-associated deaths in the United States, September-October 2009. Influenza Other Respir Viruses. 2012;6(6):e169-77.

122. Rello J, Rodriguez A, Ibanez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care. 2009;13(5):R148.

123. Riquelme R, Torres A, Rioseco ML, et al. Influenza pneumonia: a comparison between seasonal influenza virus and the H1N1 pandemic. Eur Respir J. 2011;38(1):106-11.

124. Rodriguez-Rieiro C, Carrasco-Garrido P, Hernandez-Barrera V, et al. Pandemic influenza hospitalization in Spain (2009): incidence, in-hospital mortality, comorbidities and costs. Hum Vaccin Immunother. 2012;8(4):443-7.

125. Rosen DG, Lopez AE, Anzalone ML, et al. Postmortem findings in eight cases of influenza A/H1N1. Mod Pathol. 2010;23(11):1449-57.

126. Sam I, Abdul-Murad A, Karunakaran R, et al. Clinical features of Malaysian children hospitalized with community-acquired seasonal influenza. Int J Infect Dis. 2010;14:e36-40.

127. Santa-Olalla Peralta P, Cortes-Garcia M, Vicente-Herrero M, et al. Risk factors for disease severity among hospitalised patients with 2009 pandemic influenza A (H1N1) in Spain, April - December 2009. Euro Surveill. 2010;15(38).

128. Sasbon JS, Centeno MA, Garcia MD, et al. Influenza A (pH1N1) infection in children admitted to a pediatric intensive care unit: differences with other respiratory viruses. Pediatr Crit Care Med. 2011;12(3):e136-40.

129. Schrag SJ, Shay DK, Gershman K, et al. Multistate surveillance for laboratory-confirmed, influenza-associated hospitalizations in children: 2003-2004. Pediatr Infect Dis J. 2006;25(5):395-400.

130. Scotta MC, Mattiello R, Marostica PJC, Jones MH, Martins LG, Fischer GB. Risk factors for need of mechanical ventilation in children with influenza A(H1N1)pdm09. J Pediatr (Rio J). 2013;89(5):444-9.

131. Sharma R, Agarwal S, Mehta S, et al. Profiling the mortality due to influenza A (H1N1) pdm09 at a tertiary care hospital in Jaipur during the current season--January & February 2015. J Assoc Physicians India. 2015;63(4):36-9.

132. Shin SY, Kim JH, Kim HS, et al. Clinical characteristics of Korean pediatric patients critically ill with influenza A (H1N1) virus. Pediatr Pulmonol. 2010;45(10):1014-20.

133. Sibley WA, Bamford CR, Laguna JF. Influenza vaccination in patients with multiple sclerosis. JAMA. 1976;236(17):1965-6.

134. Skarbinski J, Jain S, Bramley A, et al. Hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in the United States—September-October 2009. Clin Infect Dis. 2011;52(Suppl 1):S50-9.

135. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004;351(25):2611-8.

136. Stein M, Tasher D, Glikman D, et al. Hospitalization of children with influenza A(H1N1) virus in Israel during the 2009 outbreak in Israel: a multicenter survey. Arch Pediatr Adolesc Med. 2010;164(11):1015-22.

137. Streng A, Prifert C, Weissbrich B, Liese JG. Continued high incidence of children with severe influenza A (H1N1) pdm09 admitted to paediatric intensive care units in Germany during the first three post-pandemic influenza seasons, 2010/11–2012/13. BMC Infect Dis. 2015;15(1):573.

138. Streng A, Grote V, Liese JG. Severe influenza cases in paediatric intensive care units in Germany during the pre-pandemic seasons 2005 to 2008. BMC Infect Dis. 2011;11:233.

139. Subramony H, Lai FYL, Ang LW, Cutter JL, Lim PL, James L. An epidemiological study of 1348 cases of pandemic H1N1 influenza admitted to Singapore hospitals from July to September 2009. Ann Acad Med Singapore. 2010;39(4):283-8.

140. Tamma PD, Turnbull AE, Milstone AM, et al. Clinical outcomes of seasonal influenza and pandemic influenza A (H1N1) in pediatric inpatients. BMC Pediatr. 2010;10(1):72.

141. Thompson DL, Jungk J, Hancock E, et al. Risk factors for 2009 pandemic influenza A (H1N1)-related hospitalization and death among racial/ethnic groups in New Mexico. Am J Public Health. 2011;101(9):1776-84.

142. Tokuhira N, Shime N, Inoue M, et al. Mechanically ventilated children with 2009 pandemic influenza A/H1N1: results from the National Pediatric Intensive Care Registry in Japan. Pediatr Crit Care Med. 2012;13(5):e294-8.

143. Torun SH, Karakilic E, Akturk H, et al. Influenza in the pediatric population in Istanbul: a one center experience 2009-2014. Epidemiol Mikrobiol Imunol. 2016;65(1):46-50.

144. Tran D, Vaudry W, Moore DL, et al. Comparison of children hospitalized with seasonal versus pandemic influenza A, 2004-2009. Pediatrics. 2012;130(3):397-406.

145. Tresoldi AT, Pereira RM, Fraga AM, et al. Clinical features and outcome of children and adolescents hospitalized with influenza A (H1N1) virus infection compared with flu-like symptoms and negative rapid tests for influenza A (H1N1) admitted in the same period of time. J Trop Pediatr. 2011;57(6):481-3.

146. Uchimura T, Mori M, Nariai A, Yokota S. Analysis of cases of severe respiratory failure in children with influenza (H1N1) 2009 infection in Japan. J Infect Chemother. 2012;18(1):59-65.

147. Weigl J, Puppe W, Schmitt H. The incidence of influenza-associated hospitalizations in children in Germany. Epidemiol Infect. 2002;129(03):525-33.

148. Wie S, So BH, Song JY, et al. A comparison of the clinical and epidemiological characteristics of adult patients with laboratory-confirmed influenza A or B during the 2011-2012 influenza season in Korea: a multi-center study. PLoS ONE. 2013;8(5):e62685.

149. Wieching A, Benser J, Kohlhauser-Vollmuth C, Weissbrich B, Streng A, Liese JG. Clinical characteristics of pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Northern Bavaria, Germany. BMC Res Notes. 2012;5:304.

150. Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004-2012. Pediatrics. 2013;132(5):796-804.

151. Zheng Y, He Y, Deng J, et al. Hospitalized children with 2009 influenza a (H1N1) infection in Shenzhen, China, November-December 2009. Pediatr Pulmonol. 2011;46(3):246-52.

152. Zinman L, Thoma J, Kwong JC, Kopp A, Stukel TA, Juurlink DN. Safety of influenza vaccination in patients with myasthenia gravis: a population-based study. Muscle Nerve. 2009;40(6):947-51.

153. Cutter JL, Ang LW, Lai FYL, Subramony H, Ma S, James L. Outbreak of pandemic influenza A (H1N1-2009) in Singapore, May to September 2009. Ann Acad Med Singapore. 2010;39(4):273-10.

154. Jouvet P, Hutchison J, Pinto R, et al. Critical illness in children with influenza A/pH1N1 2009 infection in Canada. Pediatr Crit Care Med. 2010;11(5):603-9.

155. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. JAMA. 2005;294(17):2188-94.

156. Khandaker G, Zurynski Y, Buttery J, et al. Neurologic complications of influenza A(H1N1)pdm09: surveillance in 6 pediatric hospitals. Neurology. 2012;79(14):1474-81.

157. Martin-Loeches I, Sanchez-Corral A, Diaz E, et al. Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A(H1N1) virus. Chest. 2011;139(3):555-62.

158. Newland JG, Laurich VM, Rosenquist AW, et al. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. J Pediatr. 2007;150(3):306-10.

159. Sachedina N, Donaldson LJ. Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. Lancet. 2010;376(9755):1846-52.

160. Rosenthal R. The file drawer problem and tolerance for null results. Psychol Bull. 1979;86(3):638.

Appendix A: Search Strategy and Results

Table A1: Supplemental search terms for specific NNCs

Primary affected location	Disease
Central nervous system	Brain injury (traumatic, anoxic, congenital)
	Bulbar dysfunction (bulbar palsy)
	Cerebral atrophy
	Cerebral palsy
	Cerebral vasculitis (central nervous system vasculitis or angiitis)
	Cerebrovascular disease (e.g., hemorrhagic stroke, ischemic stroke, transient ischemic attack)
	Congenital anomalies, defects or malformations of the brain and spine (e.g., anencephaly, encephalocele, Dandy-Walker syndrome, holoprosencephaly, hydrocephalus, megalencephaly, microcephaly, spina bifida [Arnold-Chiari or Chiari malformation])
	Encephalopathy
	Multiple sclerosis
	Neurodegenerative conditions, including: - Amyotrophic lateral sclerosis (Lou Gehrig's disease) - Congenital neurodegenerative disease - Dementia (Alzheimer's disease) - Demyelinating disease - Huntington's disease - Parkinson's disease
	Neurodevelopmental conditions, including: - Developmental delay - Developmental disabilities (e.g., Asperger's syndrome, attention deficit hyperactivity disorder, autism, autism spectrum disorders, fetal alcohol spectrum disorders) - Intellectual disabilities (e.g., Down syndrome, fragile X syndrome, non-syndromic intellectual disabilities)
	Seizures (e.g., epilepsy, seizure disorders, febrile seizure)
	Spinal cord injury (traumatic)
	Tuberous sclerosis
Neuromuscular conditions	Hypotonia
	Muscular dystrophies (Becker, congenital, Duchenne, distal, Emery-Dreifuss, facioscapulohumeral, limb-girdle, myotonic, oculopharyngeal)
	Myasthenia gravis
	Myopathy
	Spinal muscular atrophy (autosomal recessive proximal spinal muscular atrophy)
Peripheral nervous system	Neuropathy
Other	Vocal cord paralysis

Table A2: Electronic database search sets and results

Set #	Searches	Results
MEDLINE (1946 to 25 October 2016)		
1	Influenza, Human/co, ep, mo, pa, pp, pc [Complications, Epidemiology, Mortality, Pathology, Physiopathology, Prevention & Control]	30441
2	*Influenza, Human/	36559
3	influenza.ti.	59844
4	influenza.ab. /freq=2	37834
5	or/1-4	74422
6	Comorbidity/	84653
7	(underly* or "co morbid*" or comorbid* or "pre exist*" or preexist* or existing or ((previous* or earlier or prior) adj2 diagnos*)).tw.	774358
8	or/6-7	826494
9	exp Recurrence/	163061
10	exp Disease Progression/	142594
11	("flare* up*" or flareup* or worse* or aggravat* or exacerbat* or deteriorate* or relaps* or ((increase* or more or high*) adj3 (symptom* or freq*)) or recur* or "re emerge" or reemerg* or sicken* or progressed or progression or breakthrough or "break through").tw.	1579902
12	or/9-11	1698248
13	5 and 8 and 12	463
14	(((neuro* or nerv* or PNS or CNS or demyelinat*) adj2 (disease* or condition* or disorder* or deficit* or dysfunction*)) or neurodegen*).tw.	245098
15	exp Movement Disorders/	119628
16	(parkinson* or lewy or huntington* or chorea* or d?stoni* or d?skine* or hypoton*).tw.	146679
17	Muscle Hypotonia/	3015
18	exp Motor Neuron Disease/	23471
19	(ALS or gehrig* or moto?neuro* or "motor neuro*" or neuropath* or amyotrophic lateral sclerosis or (bulbar adj2 (pals* or d?sfunction*)) or (spin* adj2 musc* adj2 atroph*)).tw.	167768
20	exp Multiple Sclerosis/	49656
21	multiple sclerosis.tw.	59752
22	exp Muscular Dystrophies/	23861
23	(musc* adj2 dystroph*).tw.	21695
24	exp neuromuscular manifestations/	46255
25	exp Myopathies, Structural, Congenital/	1049
26	(myopath* or (musc* adj2 (rigid* or spasm* or atroph* or weak*))).tw.	49532
27	exp Myasthenia Gravis/	13773
28	myasthenia gravis.tw.	12317
29	exp "malformations of cortical development"/ or exp neural tube defects/	37083
30	exp Hydrocephalus/	21536
31	(anenceph* or microceph* or megalenceph* or holoprosenceph* or hydroceph* or chiari).tw.	39144
32	exp Brain Damage, Chronic/	34099
33	exp Craniocerebral Trauma/ or exp Peripheral Nerve Injuries/ or exp Spinal Cord Injuries/	184897
34	Vocal Cord Paralysis/	5642
35	(((brain* or cere* or cord* or head*) adj2 (atroph* or injur* or trauma*)) or paraly* or parapleg* or quadripleg* or plegia* or encephalopath* or pals* or concuss*).tw.	269079
36	exp Spinal Dysraphism/	7770
37	spina bifida.tw.	6213

Set #	Searches	Results
38	exp Dementia/	138150
39	(dement* or (progressive adj2 aphasia) or alzheimer* or (cognit* adj2 (impair* or dysfunction))).tw.	204925
40	exp brain ischemia/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp stroke/	215156
41	(stroke* or ((brain* or cere*) adj2 (accident* or infarc* or isch?em* or thrombos* or h?emorrh*)) or CVA or CVAs or TIA or TIAs or transient isch?emic attack*).tw.	247404
42	exp Vasculitis, Central Nervous System/	7327
43	((cere* or CNS) adj2 (vasculitis or angiitis)).tw.	933
44	exp Epilepsy/	143747
45	(epilep* or seizure* or convuls*).tw.	178089
46	exp Intellectual Disability/	87555
47	(((intellect* or cognit*) adj2 disab*) or down syndrome or "fragile x").tw.	28986
48	Tuberous sclerosis/	5385
49	tuberous sclerosis.tw.	6592
50	exp Neurodevelopmental Disorders/	155994
51	(((neurodevelop* or develop*) adj2 (deficit* or delay* or disorder*)) or autis* or aperger* or attention deficit or ADHD).tw.	92572
52	Fetal Alcohol Spectrum Disorders/	3736
53	(((f?etal or "pre natal" or prenatal) adj2 alcohol) or FASD).tw.	4443
54	or/14-53	1851311
55	Hospitalization/	85035
56	exp Critical Care/	49400
57	exp Intensive Care Units/	66149
58	Emergency Service, Hospital/	52021
59	(hospitalis* or hospitaliz* or ((hospital* or patient*) adj3 (admit* or admiss*)) or intensive care or ICU or critical care or ((emergency or casualty) adj (room* or department*)) or A&E or "A & E" or ER).tw.	560716
60	or/55-59	650808
61	exp Pneumonia/	83129
62	pneumonia*.tw.	136800
63	or/61-62	171165
64	exp Airway Management/	100057
65	(ventilat* or tracheo* or pulmonary support*).tw.	166083
66	or/64-65	216978
67	exp Mortality/	322482
68	(fatal* or mortal* or death* or die or died or dying or dies).tw.	1348533
69	or/67-68	1493930
70	((serious or severe*) adj2 (outcome* or complication*)).tw.	54283
71	or/55-70	2287609
72	5 and 54 and 71	699
73	5 and 12 and 54	222
74	13 or 72 or 73	1246
75	comment.pt.	687189
76	letter.pt.	945014
77	editorial.pt.	421693
78	animals/	6004897
79	humans/	16407550
80	78 not (78 and 79)	4298783
81	case reports/	1832482
82	75 or 76 or 77 or 80 or 81	7387429

Set #	Searches	Results
83	74 not 82	1005
84	limit 83 to (English or French)	907
EMBASE (1974 to 25 October 2016)		
1	exp influenza/co, ep, pc, si [Complication, Epidemiology, Prevention, Side Effect]	32955
2	exp *influenza/	47390
3	influenza.ti.	63097
4	or/1-3	82115
5	*comorbidity/	14541
6	(underly* or "co morbid*" or comorbid* or "pre exist*" or preexist* or existing or ((previous* or earlier or prior) adj2 diagnos*)).ti,kw.	59249
7	or/5-6	60366
8	*recurrent disease/	11703
9	*disease exacerbation/	4388
10	*relapse/	15924
11	*disease course/	14609
12	("flare* up*" or flareup* or worse* or aggravat* or exacerbat* or deteriorate* or relaps* or ((increase* or more or high*) adj3 (symptom* or freq*)) or recur* or "re emerge" or reemerg* or sicken* or progressed or progression or breakthrough or "break through").ti,kw.	323825
13	or/8-12	333624
14	4 and 7 and 13	3
15	(((neuro* or nerv* or PNS or CNS or demyelinat*) adj2 (disease* or condition* or disorder* or deficit* or dysfunction*)) or neurodegen*).ti,kw.	74345
16	(parkinson* or lewy or huntington* or chorea* or d?stoni* or d?skine* or hypoton*).ti,kw.	126322
17	(ALS or gehrig* or moto?neuro* or "motor neuro*" or neuropath* or amyotrophic lateral sclerosis or (bulbar adj2 (pals* or d?sfunction*)) or (spin* adj2 musc* adj2 atroph*)).ti,kw.	107164
18	multiple sclerosis.ti,kw.	63012
19	(myopath* or (musc* adj2 (rigid* or spasm* or atroph* or weak*))).ti,kw.	25399
20	(musc* adj2 dystroph*).ti,kw.	17839
21	myasthenia gravis.ti,kw.	11309
22	(anenceph* or microceph* or megalenceph* or holoprosenceph* or hydroceph* or chiari).ti,kw.	25762
23	(((brain* or cere* or cord* or head*) adj2 (atroph* or injur* or trauma*)) or paraly* or parapleg* or quadripleg* or plegia* or encephalopath* or pals* or concuss*).ti,kw.	188254
24	spina bifida.ti,kw.	4470
25	tuberous sclerosis.ti,kw.	5536
26	(stroke* or ((brain* or cere*) adj2 (accident* or infarc* or isch?em* or thrombos* or h?emorrh*)) or CVA or CVAs or TIA or TIAs or transient isch?emic attack*).ti,kw.	185066
27	((cere* or CNS) adj2 (vasculitis or angiitis)).ti,kw.	657
28	(epilep* or seizure* or convuls*).ti,kw.	147118
29	(dement* or (progressive adj2 aphasia) or alzheimer* or (cognit* adj2 (impair* or dysfunction))).ti,kw.	167200
30	(((intellect* or cognit*) adj2 disab*) or down syndrome or "fragile x").ti,kw.	24373
31	(((neurodevelop* or develop*) adj2 (deficit* or delay* or disorder*)) or autis* or aperger* or attention deficit or ADHD).ti,kw.	63380
32	(((f?etal or "pre natal" or prenatal) adj2 alcohol) or FASD).ti,kw.	4628
33	or/15-32	1151021
34	*hospitalization/	33220
35	*intensive care/	68022

Set #	Searches	Results
36	*intensive care unit/	35618
37	exp *emergency care/	12274
38	*emergency ward/	29098
39	(hospitalis* or hospitaliz* or ((hospital* or patient*) adj3 (admit* or admiss*)) or intensive care or ICU or critical care or ((emergency or casualty) adj (room* or department*)) or A&E or "A & E" or ER).ti,kw.	192107
40	exp *pneumonia/	99409
41	pneumonia*.ti,kw.	81804
42	exp *assisted ventilation/	50428
43	(ventilat* or tracheo* or pulmonary support*).ti,kw.	84328
44	exp *mortality/	140360
45	(fatal* or mortal* or death* or die or died or dying or dies).ti,kw.	336297
46	((serious or severe*) adj2 (outcome* or complication*)).ti,kw.	3922
47	or/34-46	823924
48	4 and 33 and 47	52
49	4 and 13 and 47	97
50	14 or 48 or 49	152
51	note.pt.	659206
52	letter.pt.	958415
53	editorial.pt.	520088
54	exp animal/	22563868
55	human/	17953630
56	54 not (54 and 55)	4610238
57	case report/	2154775
58	51 or 52 or 53 or 56 or 57	8585653
59	50 not 58	108
60	limit 59 to (English or French)	98

Appendix B: Level of Evidence Based on Research Design and Quality (Internal Validity) Rating of Evidence

Table B1: Definition of overall study quality

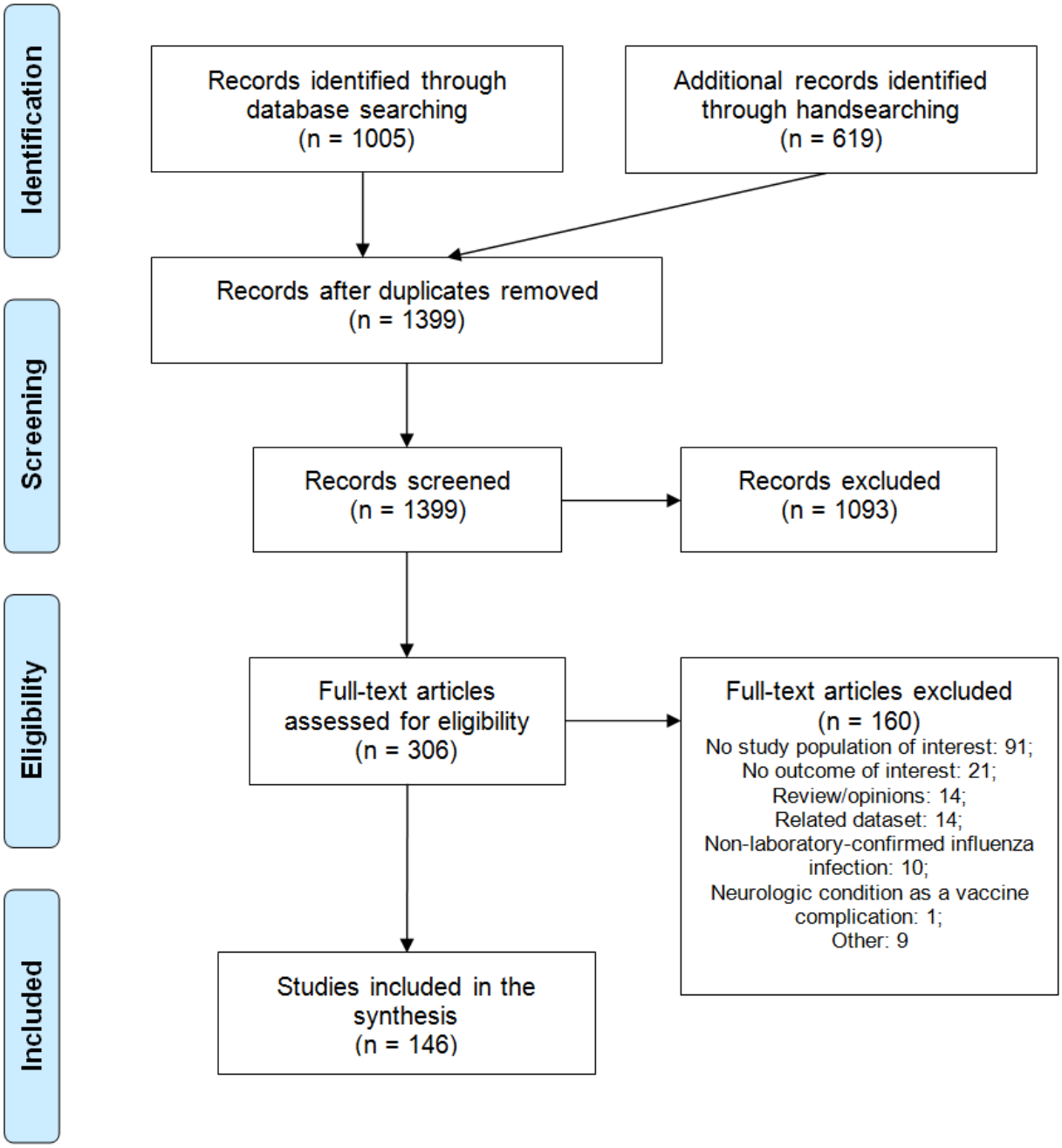
Good	A study (including meta-analyses or systematic reviews) that meets all design-specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design-specific criteria are outlined in Harris et al. (2001)[7].

Table B2: Levels of evidence based on research design

I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Appendix C: Flow Diagram



Appendix D: Summary of Evidence Related to Risk of Serious Influenza-Related Complications in Individuals with Neurologic or Neurodevelopment Conditions

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Ahrens JO, Morrow BM, Argent AC. Influenza A(H1N1)pdm09 in critically ill children admitted to a paediatric intensive care unit, South Africa. Southern African Journal of Critical Care. 2015;31(1):4-7.(8)	Design: Clinical case series (single centre) Period: August–September 2009 Location: South Africa	Case definition: Patient (children; age range not defined) admitted to ICU with laboratory-confirmed respiratory virus infection, including influenza Viral testing: Multiplex RT-PCR, subtype-specific rtRT-PCR, or respiratory viral PCR	Pandemic influenza A(H1N1)pdm09	n=19 ICU cases with pandemic influenza A(H1N1)pdm09 infection (n=5 [26.3%] fatal ICU cases) Age group: Children Median age at death: 1.5 years (range: 0.3–8.3 years)	**ICU death** n=0 of 5 (0%) fatal ICU cases had a neurologic condition (n=4 [80.0%] fatal ICU cases had at least one comorbidity).	Level III n/a
Al Soub H, Ibrahim AS, Al Maslamani M, Al-khal AL, Shaath S, Hamza NA. Epidemiology, risk factors, clinical features, and outcome of adult patients with severe pandemic A/H1N1/2009 influenza in Qatar: a retrospective study. Infect Dis Clin Pract. 2014;22(6):339-43.(9)	Design: Clinical case series (single centre) Period: July 2009–January 2011 Location: Qatar	Case definition: Patient admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=40 ICU cases Age group: Predominantly adults Mean age at ICU admission: 42.7 years (range: 15–72 years)	**ICU admission** n=2 of 40 (5.0%) ICU cases had cerebrovascular disease (82.5% of ICU cases had one or more risk factors).	Level III n/a
Al Subaie SS, Al Saadib MM. Features associated with severe disease in hospitalized children with 2009 influenza A (H1N1) infection at a university hospital in Riyadh, Saudi Arabia. Ann Saudi Med.	Design: Clinical case series (single centre) Period: July–December 2009 Location:	Case definition: Patient (≤12 years of age) hospitalized with laboratory-confirmed influenza virus infection Presentation: ILI (oral temperature of >38°C) or a history of fever or chills and at least one	Pandemic influenza A(H1N1)pdm09	n=50 hospitalized cases (n=5 [10.0%] ICU cases) Age group: Children Median age at hospitalization: 3 years (range: <0.1–12 years)	**Hospitalization** n=7 of 50 (14.0%) hospitalized cases had a pre-existing neurologic disorder (n=35 [70.0%] hospitalized cases had any pre-existing condition). **ICU admission** n=4 of 5 (80.0%) ICU cases	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
2012;32(1):53-8.[10]	Saudi Arabia	influenza-like symptom) Viral testing: rtRT-PCR			had a pre-existing neurologic disorder, including cerebral palsy (n=3) and seizure disorder (n=2) (n=5 [100.0%] ICU cases had at least one underlying condition).	
Altmann M, Fiebig L, Soyka J, von Kries R, Dehnert M, Haas W. Severe cases of pandemic (H1N1) 2009 in children, Germany. Emerg Infect Dis. 2011;17(2):186-92.[11]	Design: Population case series Period: August 2009–April 2010 Location: Germany	Case definition: Patient (<15 years of age) admitted to ICU or died with laboratory-confirmed influenza virus infection Viral testing: Antigen detection, RT-PCR, or virus isolation	Pandemic influenza A(H1N1)pdm09	n=93 ICU or fatal cases (n=15 [16.1%] fatal cases, including 4 not admitted to ICU; n=89 [95.7%] ICU or fatal cases with available information on underlying health status) Age group: Children Median age at ICU admission or death: 4.5 years (IQR: 1.3–9.3 years)	**ICU admission or death** n=51 of 89 (57.3%) ICU or fatal cases had underlying neurodevelopmental disorders (n=67 [75.3%] ICU or fatal cases had at least one underlying chronic medical condition). **ICU death** n=7 of 10 (70.0%) fatal ICU cases had underlying neurodevelopmental disorders (n=7 of 9 [77.8%%] fatal ICU cases had at least one underlying chronic medical condition). Underlying neurodevelopmental disorder was not significantly associated with death in patients admitted to ICU (OR: 2.0, 95% CI: 0.4–13.1, p=0.501).	Level III n/a
Ampofo K, Gesteland PH, Bender J, et al. Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection. Pediatrics.	Design: Clinical case series (single centre) Period: July 2001–June 2002, July 2002–June	Case definition: Patient (≤18 years of age) hospitalized with community-acquired, laboratory-confirmed influenza virus infection Viral testing: 7-valent DFA test, with viral	Seasonal influenza A and B (2001–2002 through 2003–2004) n=285 of 325 (87.6%) hospitalized	n=325 hospitalized cases Age group: Children Age at hospitalization: n=325 of 325 (100.0%) hospitalized cases <18 years of age	**Hospitalization** n=28 of 325 (8.6%) hospitalized cases had underlying neurological and neuromuscular conditions, including seizure disorder (n=15), cerebral palsy (n=8), spina bifida (n=3), myotonic and muscular dystrophy	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
2006;118(6):2409-17.[12]	2003, and July 2003–June 2004 Location: USA	culture performed on DFA-negative samples Risk group definition: ACIP	cases infected with influenza A, 40 (12.3%) with influenza B, and 1 (0.1%) with influenza A and B		(n=3), and other conditions (n=7), such as traumatic brain injury, traumatic spinal cord injury, bulbar dysfunction, vocal cord paralysis, developmental delay, and encephalopathy (n=120 [36.9%] hospitalized cases had an ACIP-defined high-risk chronic medical condition).	
Angelo SJ, Marshall PS, Chrissoheris MP, Chaves AM. Clinical characteristics associated with poor outcome in patients acutely infected with influenza A. Connecticut Medicine. 2004;68(4):199-205.[13]	Design: Clinical case series (single centre) Period: 1998–1999 Location: USA	Case definition: Patient (≥18 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: DFA test	Seasonal influenza A (1998–1999)	n=132 hospitalized cases (n=27 [20.5%] fatal cases and/or cases who developed respiratory failure or shock) Age group: Adults Mean age at hospitalization: 77 years	**Hospitalization** n=34 of 132 (25.8%) hospitalized cases had a history of stroke or TIA and 23 (17.4%) had a history of dementia. **Death and/or respiratory failure** n=12 of 27 (44.4%) fatal cases and/or cases who developed respiratory failure or shock had a history of stroke or TIA and 5 (18.5%) had a history of dementia. History of stroke or TIA was a significant predictor of death and/or respiratory failure or shock among hospitalized cases in univariate (OR: 3.0, p=0.01) and multivariate (p=0.018) analyses.	Level III n/a
Arnheim-Dahlström L, Hällgren J, Weibull CE, Sparén P. Risk of presentation to hospital with epileptic seizures	Design: Population self-controlled case series	Case definition: Vaccinated individual with or without previous epilepsy, according to diagnosis of epilepsy or	Monovalent AS03-adjuvanted pandemic A(H1N1)pdm09	n=7787 pandemic influenza vaccine recipients with epilepsy and 356,611 without epilepsy (n=738 [9.5%] with epilepsy	**Post-vaccination (exacerbation)** There was no increased risk of seizures in vaccinated individuals with previously	Level III n/a-

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
after vaccination with monovalent AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix): self controlled case series study. BMJ. 2012;345:e7594.(14)	Period: October 2009–May 2010 Location: Sweden (three counties)	prescription of anti-epileptic drugs within one year before the control period (90 to 30 days) before vaccination Influenza vaccination status: Registry record	influenza vaccine	experienced seizures and 121 [0.03%] without epilepsy experience seizures) Age group: Mixture of children and adults Mean age at vaccination (SD): 41 (25) years (did not differ significantly between those with and without epilepsy)	diagnosed epilepsy during the first (day 1 [vaccination day] to day 7 after vaccination; relative incidence: 1.01, 95% CI: 0.74–1.39) or second (day 8 to day 30 after vaccination; relative incidence: 1.00, 95% CI: 0.83–1.21) risk period compared to the control period (90 to 30 days before vaccination and 31 to 90 days after vaccination).	
Auriel E, Regev K, Dori A, Karni A. Safety of influenza and H1N1 vaccinations in patients with myasthenia gravis, and patient compliance. Muscle Nerve. 2011;43(6):893-4.(15)	Design: Clinical case series (multi-centre) Period: December 2009–February 2010 (vaccine receipt) Location: Israel	Case definition: Patient (≥18 years of age) diagnosed with MG, excluding patients pregnant during survey period or with other myasthenic syndromes Influenza vaccination status: Questionnaire	Seasonal influenza vaccine and/or pandemic influenza A(H1N1)pdm09 vaccine n=38 of 74 (51.4%) MG patients received the seasonal influenza vaccine, 24 (32.4%) received the pandemic influenza A(H1N1)pdm09 vaccine, and 20 (27.0%) received both vaccines	n=74 seasonal and/or pandemic influenza vaccines recipients with MG Age group: Adults Mean age of all vaccine recipients (SD): 60.5 (18.7) years	**Post-vaccination (exacerbation)** n=0 of 74 (0%) MG patients reported having a myasthenic exacerbation following seasonal and/or pandemic influenza vaccination after ≥8 weeks of follow-up.	Level III n/a
Bagdure D, Curtis DJ, Dobyns E, Glodé MP, Dominguez SR.	Design: Clinical case series (single	Case definition: Patient hospitalized with laboratory-confirmed	Pandemic influenza A(H1N1)pdm09	n=307 hospitalized pandemic cases (n=80 [26.1%] pandemic ICU	**Hospitalization (pandemic)** n=74 of 307 (24.1%) hospitalized pandemic cases	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Hospitalized children with 2009 pandemic influenza A (H1N1): comparison to seasonal influenza and risk factors for admission to the ICU. PLoS One. 2010;5(12):e15173.[16]	centre) Period: December 2008–May 2009 (seasonal) and May–November 2009 (pandemic) Location: USA	influenza virus infection Viral testing: DFA test, immunoassay, or RT-PCR (samples positive by DFA test or immunoassay, but negative by RT-PCR were excluded)	Seasonal influenza A and B (2008–2009)	cases) and 89 hospitalized seasonal cases Age group: Predominantly children Median age at hospitalization: 6.0 years (IQR: 2.4–10.2 years; n=300 of 307 [97.7%] hospitalized pandemic cases ≤18 years of age) for pandemic cases and 1.8 years (IQR: 0.7–8.5 years) for seasonal cases Median age at ICU admission for pandemic cases: 6.7 years (IQR: 4.1–11.7 years; n=77 of 80 [96.3%] pandemic ICU cases ≤18 years of age)	had any underlying neurologic disorder, including seizure disorder (n=37), cerebral palsy (n=25), cognitive/developmental impairment (n=57), or other neurologic disease (n=37) (n=203 [66.1%] hospitalized pandemic cases had any underlying medical condition). **ICU admission (pandemic)** n=30 of 80 (37.5%) pandemic ICU cases had any underlying neurologic disorder, including seizure disorder (n=17), cerebral palsy (n=10), cognitive/developmental impairment (n=24), and other neurologic disease (n=13) (n=57 [71.3%] pandemic ICU cases had any underlying medical condition). Pandemic ICU cases were significantly more likely to have any underlying neurological disorder (p=0.002), seizure disorder (p=0.01), and cognitive/developmental impairment (p=0.01), but not cerebral palsy (p=0.15) or other neurologic disease (p=0.23) compared to pandemic cases not admitted to ICU.	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Hospitalization (seasonal) n=25 of 89 (28.1%) hospitalized seasonal cases had any underlying neurologic disorder, including seizure disorder (n=9), cerebral palsy (n=7), cognitive/developmental impairment (n=21), or other neurologic disease (n=17) (n=46 [51.7%] hospitalized seasonal cases had any underlying medical condition). **Pandemic vs. seasonal (hospitalization)** Pandemic influenza A(H1N1)pdm09 cases were not significantly more likely to have any underlying neurological disorder (p=0.49), seizure disorder (p=0.71), cerebral palsy (p=1.0), cognitive/developmental impairment (p=0.36), or other neurological condition (p=0.11) compared to seasonal influenza A and B cases.	
Balanzat AM, Hertlein C, Apezteguia C, et al. An analysis of 332 fatalities infected with pandemic 2009 influenza A (H1N1) in Argentina. PLoS One. 2012;7(4):e33670.[17]	Design: Population case series Period: June–July 2009 Location: Argentina	Case definition: Death associated with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09	n=332 fatal cases Age group: Predominantly adults Median age at death: 36 years (IQR: 13–53 years; n=93 of 332 [28.0%] fatal cases ≤18 years of age)	**Death** n=54 of 301 (17.9%) fatal cases had neurologic disease (n=239 of 319 [74.9%] fatal cases had at least one comorbidity). Underlying neurologic disease was more common in younger (<5 and 5–49	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					years of age) compared to older (≥50 years of age) fatal cases (18.8, 20.6, and 12.9%, respectively).	
Barakat A, Ihazmad H, El Falaki F, Tempia S, Cherkaoui I, El Aouad R. 2009 Pandemic influenza A virus subtype H1N1 in Morocco, 2009–2010: epidemiology, transmissibility, and factors associated with fatal cases. J Infect Dis. 2012;206(suppl 1):S94-100.[18]	Design: Population case series Period: June 2009–February 2010 Location: Morocco	Case definition: Outpatient (ILI) or inpatient (SARI) with or without laboratory-confirmed influenza virus infection Presentation: 1) ILI: fever (≥38°C) and cough or sore throat in the absence of a specific diagnosis and with symptom onset <5 days prior to presentation; or sudden onset of ≥1 respiratory sign (cough, difficulty breathing, rhinitis, or coryza) and ≥1 general symptom (fever, headache, fatigue, or myalgia) <5 days before presentation; 2) SARI (≥5 years of age): fever (>38°C), cough, and shortness of breath or difficulty breathing with a duration of illness of <7 days; 3) SARI (2 months–5 years of age): cough or difficulty breathing, with or without wheezing and stridor in a calm child, or chest indrawing; or 4) SARI (1 week–<2 months): respiratory illness with	Pandemic influenza A(H1N1)pdm09	n=1398 ILI/SARI cases with pandemic influenza A(H1N1)pdm09 infection (n=1056 [75.5%] ILI and 342 [24.5%] SARI cases, including 64 fatal SARI cases) Age group: Mixture of children and adults Age of hospitalized (SARI) cases: n=210 of 342 [61.4%] SARI cases <25 years of age	**Hospitalization** n=11 of 342 (3.2%) hospitalized (SARI) cases with pandemic influenza A(H1N1)pdm09 had an underlying neurologic disorder. **Death** n=4 of 64 (6.3%) fatal hospitalized (SARI) cases with pandemic influenza A(H1N1)pdm09 had an underlying neurologic disorder. Neurologic disorder was a significant risk factor for mortality among hospitalized (SARI) cases with pandemic influenza A(H1N1)pdm09 (age-aOR: 7.5, 95% CI: 1.5–36.4, p=0.013).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		one of the following signs: convulsions, tachypnea, chest indrawing, nasal flaring, grunting, lethargy or unconsciousness, fever (>38°C or warm to the touch), or hypothermia (<36°C or cold to the touch) Viral testing: rtRT-PCR				
Bassetti M, Parisini A, Calzi A, et al. Risk factors for severe complications of the novel influenza A (H1N1): analysis of patients hospitalized in Italy. Clin Microbiol Infect. 2011;17(2):247-50.(19)	Design: Clinical case series (multi-centre) Period: July–November 2009 Location: Italy	Case definition: Patient hospitalized for ≥24 hours with laboratory-confirmed influenza virus infection Presentation: Fever (≥38°C) and cough or sore throat or other symptoms consistent with influenza) Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=81 hospitalized cases (n=10 [12.3%] ICU or fatal cases) Age group: Predominantly adults (hospitalization); adults (ICU admission or death) Median age at hospitalization: 32 years (range: 1–81 years; n=16 of 81 [19.8%] hospitalized cases <18 years of age) Median age at ICU admission or death: 43.5 years (range: 20–79 years)	**Hospitalization** n=9 of 81 (11.1%) hospitalized cases had underlying neurocognitive disorder (n=56 [69.1%] hospitalized cases had an underlying medical condition). **ICU admission or death** n=3 of 10 (30.0%) ICU or fatal cases had underlying neurocognitive disorders (n=10 [100.0%] ICU or fatal cases had an underlying medical condition). Underlying neurocognitive disorder was significantly associated with severe disease (ICU admission or death) among hospitalized cases (p=0.02). Neurocognitive disorders include Alzheimer's disease, vascular neurocognitive disorder, schizophrenia, and frontotemporal degeneration	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Bennet R, Hamrin J, Wirgart BZ, Östlund MR, Örtqvist Å, Eriksson M. Influenza epidemiology among hospitalized children in Stockholm, Sweden 1998-2014. Vaccine. 2016;34(28):3298-302.[20]	Design: Clinical case series (single centre) Period: 1998–2014 Location: Sweden	Case definition: Patient (<18 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: Immunofluorescence and viral isolation before and rtRT-PCR after October 2007	Seasonal influenza A and B and pandemic influenza A(H1N1)pdm09 (1998–1999 through 2013–2014, including pandemic influenza season) n=557 of 922 (60.4%) hospitalized cases infected with non-pandemic influenza A, 179 (19.4%) with influenza B, and 186 (20.2%) with influenza A(H1N1)pdm09, including 93 from pandemic season	n=922 hospitalized cases Age group: Children	**Hospitalization** n=131 of 922 (14.2%) hospitalized cases had neuromuscular disease (n=312 [33.8%] hospitalized cases had previously known risk factors).	Level III n/a
Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. N Engl J Med. 2005;353(24):2559-67.[21]	Design: Population case series Period: September 2003–May 2004 Location: USA	Case definition: Death associated with laboratory-confirmed influenza virus infection in patients <18 years of age Viral testing: One or more of the following: enzyme immunoassay, immunohistochemistry, direct or indirect immunofluorescent antibody staining, RIDT,	Seasonal influenza A and B (2003–2004) n=126 of 153 (82.4%) fatal cases with typed influenza viruses: n=123 of 126 (97.6%) infected with influenza A (n=39 [31.0%] subtyped: all	n=153 fatal cases (n=149 [97.4%] fatal cases with available information on underlying health status) Age group: Children Median age at death: 3 years (range: <0.1–17 years)	**Death** n=49 of 149 (32.9%) fatal cases had underlying chronic neurologic or neuromuscular conditions (n=34 [69.4%] with ≥1 neurologic condition), including developmental delay (n=42), seizure disorder (n=23), and cerebral palsy (n=14) (n=79 [53.0%] fatal cases had an ACIP-defined high-risk or other chronic medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		RT-PCR, and viral culture (n=63 of 153 [41.2%] cases determined by multiple testing methods) Risk group definition: ACIP (before inclusion of neurologic disease in children) and other chronic conditions (includes neurological disease)	influenza A[H3N2]) and 3 (2.4%) with influenza B			
Blanton L, Peacock G, Cox C, Jhung M, Finelli L, Moore C. Neurologic disorders among pediatric deaths associated with the 2009 pandemic influenza. Pediatrics. 2012;130(3):390-6.(22) *(Dataset overlaps with Cox CM, et al. Clin Infect Dis. 2011;52 Suppl 1:S69-74.(39) [Pandemic deaths])*	Design: Population case series Period: April 2009–September 2010 Location: USA	Case definition: Death associated with laboratory-confirmed influenza virus infection in patients <18 years of age Viral testing: RT-PCR (88%), RIDT (8%), fluorescent antibody test, enzyme immunoassay, immunohistochemistry, or viral culture with subtyping performed as needed (n=57 of 343 [16.6%] cases with undetermined subtype classified as probable pandemic influenza A[H1N1]pdm09 infection) Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09	n=343 fatal cases (n=336 [98.0%] fatal cases with available information on underlying health status) Age group: Children	**Death** n=146 of 336 (43.5%) fatal cases had underlying neurologic disorders (n=71 [48.6%] with >1 neurologic disorder), including neurodevelopmental disorders (n=137), epilepsy (n=74), and neuromuscular disorders (n=9). Neurodevelopmental disorders include intellectual disability (n=111), cerebral palsy (n=51), hydrocephalus with ventriculoperitoneal shunt (n=16), and autism (n=3). Neuromuscular disorders include muscular dystrophy (n=6) and mitochondrial disorders (n=3) (n=227 [67.6%] fatal cases had at least one high-risk condition). Fatal cases with neurologic disorder (n=146) were significantly more likely to die in the hospital after	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					admission (p<0.01), have complications occur during their illness (p<0.01), and develop radiographically confirmed pneumonia (p<0.01), ARDS (p=0.03), and seizures (p=0.04), but less likely to develop shock (p<0.01) and sepsis (p<0.01) than children without high-risk conditions (n=109).	
Blumental S, Huisman E, Cornet MC, Ferreiro C, De Schutter I, Reynders M. Pandemic A/H1N1v influenza 2009 in hospitalized children: a multicenter Belgian survey. BMC Infect Dis. 2011;11:313.[23]	Design: Clinical case series (multi-centre) Period: July 2009–January 2010 Location: Belgium	Case definition: Patient (≤18 years of age) hospitalized with laboratory-confirmed influenza virus infection Presentation: Fever and/or respiratory signs/symptoms Viral testing: rtRT-PCR for A(H1N1)pdm09 (proven cases) or antigen and/or positive culture for influenza A (probable cases)	Pandemic influenza A(H1N1)pdm09	n=215 hospitalized cases (n=21 [9.8%] ICU cases and 5 [2.3%] fatal cases) Age group: Children Median age at hospitalization: 2.6 years (range: <0.1–17.3 years) Median age at ICU admission: 6.3 years (IQR: 3.9–10.8 years)	**Hospitalization** n=31 of 215 (14.4%) hospitalized cases had neurological disease (n=101 [47.0%] hospitalized cases had at least one chronic comorbid condition). **ICU admission** n=5 of 21 (23.8%) ICU cases had neurological disease (n=13 [61.9%] ICU cases had at least one chronic comorbid condition). **Death** n=5 of 5 (100.0%) fatal cases had neurological disease, including extensive CNS glioma, polymalformative syndrome, Hurler syndrome, cerebral palsy, and severe encephalopathy with pontocerebellar hypoplasia.	Level III n/a
Brink M, Hagberg L, Larsson A, Gedeborg R. Respiratory support during the influenza A	Design: Population case series	Case definition: Patient admitted to ICU with laboratory-confirmed influenza virus infection	Pandemic influenza A(H1N1)pdm09	n=126 ICU cases (n=21 [16.7%] fatal ICU cases) Age group: Predominantly	**ICU admission** n=7 of 122 (5.7%) ICU cases had neuromuscular disease (n=50 of 123 [40.7%] ICU	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
(H1N1) pandemic flu in Sweden. Acta Anaesthesiol Scand. 2012;56(8):976-86.(24)	Period: August 2009–February 2010 Location: Sweden	Viral testing: NR		adults Median age at ICU admission: 44 years (IQR: 28–56 years; n=16 of 126 [12.7%] ICU cases <16 years of age)	cases had any major comorbidity). **ICU death** n=2 of 20 (10.0%) fatal ICU cases had neuromuscular disease (n=18 of 21 [85.7%] fatal ICU cases had any major comorbidity).	
Brocklebank JT, Court SD, McQuillin J, Gardner PS. Influenza-A infection in children. Lancet. 1972;2(7776):497-500.(25)	Design: Clinical case series (multi-centre) Period: December 1971–March 1972 Location: UK	Case definition: Patient (children; age range not defined) hospitalized with laboratory-confirmed influenza virus infection Viral testing: Fluorescent antibody test	Seasonal influenza A (1971–1972)	n=77 hospitalized cases Age group: Children Age at hospitalization: n=77 of 77 (100.0%) hospitalized cases <14 years of age	**Hospitalization** n=2 of 77 (2.6%) hospitalized cases had cerebral palsy and 3 (3.9%) had severe mental subnormality (n=23 [29.9%] hospitalized cases had possible predisposing malformations and disease).	Level III n/a
Burton C, Vaudry W, Moore D, et al. Burden of seasonal influenza in children with neurodevelopmental conditions. Pediatr Infect Dis J. 2014;33(7):710-4.(6)	Design: Clinical case series (multi-centre) Period: September 2004–March 2009 Location: Canada	Case definition: Patient (≤16 years of age) hospitalized with community-acquired, laboratory-confirmed influenza virus infection Presentation: Respiratory symptoms for viral infection Viral testing: Immunofluorescence assay, RT-PCR, or viral culture Risk group definition: NACI ("vaccine indication," e.g., airway compromise)	Seasonal influenza A and B (2004–2005 through 2008–2009)	n=1991 hospitalized cases (n=261 [13.1%] ICU cases, 153 [7.7%] mechanically ventilated cases, and 14 [0.7%] fatal cases) Age group: Children	**Hospitalization** n=293 of 1991 (14.7%) hospitalized cases had underlying neurologic and neurodevelopmental conditions, including 178 with vaccine indications (n=1114 [56.0%] hospitalized cases had underlying conditions). Cases with neurologic and neurodevelopmental conditions without vaccine indications had a significantly shorter length of hospital stay than cases with vaccine indications with (p<0.001) and without (p=0.03) neurologic and neurodevelopmental	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					conditions. **ICU admission** n=73 of 261 (28.0%) ICU cases had underlying neurologic and neurodevelopmental conditions, including 49 with vaccine indications (n=178 [68.2%] ICU cases had underlying conditions). **Mechanical ventilation** n=53 of 153 (34.6%) mechanically ventilated cases had underlying neurologic and neurodevelopmental conditions, including 36 with vaccine indications (n=98 [64.1%] mechanically ventilated cases had underlying conditions). Cases with neurologic and neurodevelopmental conditions without vaccine indications required significantly more ICU admission (OR: 1.96, 95% CI: 1.18–3.27, p=0.02) and mechanical ventilation (OR: 3.70, 95% CI: 1.95–7.01, p<0.001) than cases with vaccine indications without neurologic and neurodevelopmental conditions, but not cases with vaccine indications with neurologic and neurodevelopmental	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					conditions (i.e., no significant difference in rates of ICU admission or mechanical ventilation between cases with neurologic and neurodevelopmental conditions with or without vaccine indications). Cases with neurologic and neurodevelopmental conditions with vaccine indications had a significantly longer median length of ICU stay than cases with neurologic and neurodevelopmental conditions without vaccine indications ($p<0.001$). No difference was observed in median length of ICU stay between cases with neurologic and neurodevelopmental conditions without vaccine indications and cases with vaccine indications without neurologic and neurodevelopmental conditions. **Death** n=8 of 14 (57.1%) fatal cases had underlying neurologic and neurodevelopmental conditions, including seven with vaccine indications: severe cerebral palsy, Leigh's disease associated with seizures, hypoxic	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					ischemic encephalopathy associated with seizures, severe anoxic brain injury requiring permanent tracheostomy, and severe seizure disorder requiring institutionalization (n=9 [64.3%] fatal cases had underlying conditions).	
Calitri C, Gabiano C, Garazzino S, et al. Clinical features of hospitalised children with 2009 H1N1 influenza virus infection. Eur J Pediatr. 2010;169(12):1511-5.(26)	Design: Clinical case series (single centre) Period: August–December 2009 Location: Italy	Case definition: Patient (children; age range not defined) hospitalized with ILI and laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=63 hospitalized cases Age group: Children Median age at hospitalization: 4.3 years (range: 0.07–15 years)	**Hospitalization** n=2 of 63 (3.2%) hospitalized cases had pre-existing encephalopathy (n=29 [46.0%] hospitalized cases had pre-existing chronic diseases)	Level III n/a
Campbell CN, Mytton OT, McLean EM, et al. Hospitalization in two waves of pandemic influenza A (H1N1) in England. Epidemiol Infect. 2011;139(10):1560-9.(27)	Design: Population case series Period: April 2009–January 2010 Location: UK (England)	Case definition: Patient hospitalized with laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=2416 hospitalized cases (n=2209 [91.4%] hospitalized cases with available information on underlying health status) Age group: Mixture of children and adults Median age at hospitalization: 20 years (IQR: 6–38 years; n=1373 of 2380 [57.7%] hospitalized cases <25 years of age)	**Hospitalization** n=120 of 2021 (5.9%) hospitalized cases (6 months to 64 years of age) had chronic neurological disease (n=1016 [50.3%] hospitalized cases had any pre-existing condition). Cases (6 months to 64 years of age) with chronic neurological disease had significantly higher risk of hospitalization compared to individuals without pre-existing conditions (age-aRR: 14.3, 95% CI: 11.8–17.2).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Attributable fraction among exposed (chronic neurological disease): 84.3%. Population attributable fraction (chronic neurological disease): 5.0%.	
Cardeñosa N, Rodés A, Follia N, et al. Epidemiological analysis of severe hospitalized 2009 pandemic influenza A (H1N1) cases in Catalonia, Spain. Hum Vaccin. 2011;7 Suppl:226-9.[28]	Design: Population case series Period: April 2009–January 2010 Location: Spain (Catalonia)	Case definition: Patient hospitalized with severe disease (hospitalized pneumonia, multi-organic failure, septic shock, admission to ICU, or death while hospitalized) and laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=771 hospitalized severe cases (e.g., ICU admission or death) Age group: Predominantly adults (subgroup reporting for hospitalization outcome for children <15 years of age and adults ≥15 years of age) Median age at hospitalization for severe disease: 40 years (range: 0–89 years; n=168 of 771 [21.8%] hospitalized severe cases <15 years of age)	**Hospitalization for severe disease, including ICU admission or death** n=45 of 613 (7.3%) hospitalized severe cases had cognitive disorders, 28 of 679 (4.1%) had epilepsy, and 25 of 609 (4.1%) had neuromuscular disorders (71% of hospitalized severe cases had underlying conditions). **Hospitalization for severe disease, including ICU admission or death (<15 years of age)** n=13 of 128 (10.2%) hospitalized severe cases had cognitive disorders, 13 of 149 (8.7%) had epilepsy, and 9 of 126 (7.1%) had neuromuscular disorders (62% of hospitalized severe cases had underlying conditions). **Hospitalization for severe disease, including ICU admission or death (≥15 years of age)** n=32 of 485 (6.6%) hospitalized severe cases	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					had cognitive disorders, 15 of 530 (2.8%) had epilepsy, and 16 of 483 (3.3%) had neuromuscular disorders.	
Centers for Disease Control and Prevention (CDC). Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection - United States, April-August 2009. MMWR Morb Mortal Wkly Rep. 2009;58(34):941-7.[29]	Design: Population case series Period: April–August 2009 Location: USA	Case definition: Death associated with laboratory-confirmed influenza virus infection in patients <18 years of age Viral testing: RT-PCR Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09	n=36 fatal cases Age group: Children Median age at death: 9 years (range: 0.2–17 years)	**Death** n=22 of 36 (61.1%) fatal cases had neurodevelopmental conditions (e.g., developmental delay, cerebral palsy, autism, congenital neurologic disorders, other chronic CNS disorders), including 13 with more than one neurodevelopmental diagnosis and 9 with neurodevelopmental and chronic pulmonary conditions (n=24 [66.7%] fatal cases had at least one ACIP-defined high-risk chronic medical condition).	Level III n/a
Chacon R, Mirza S, Rodriguez D, et al. Demographic and clinical characteristics of deaths associated with influenza A(H1N1) pdm09 in Central America and Dominican Republic 2009-2010. BMC Public Health. 2015;15:734.[30]	Design: Population case series Period: May 2009–June 2010 Location: Central America (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama)	Case definition: Death within two weeks of SARI with laboratory-confirmed influenza virus infection Presentation: SARI: sudden onset fever (≥38°C), cough or sore throat, and shortness of breath or difficulty breathing requiring hospitalization Viral testing: Immunofluorescence and rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=183 fatal cases Age group: Predominantly adults (subgroup reporting for death outcome for children <18 years of age and adults ≥18 years of age) Median age at death: 32 years (IQR: 18–46 years; n=46 [25.1%] fatal cases <18 years of age)	**Death** n=11 of 183 (6.0%) fatal cases had seizure disorders and 7 (3.8%) had cerebral palsy (n=112 [61.2%] fatal cases had a pre-existing medical condition). **Death (<18 years of age)** n=7 of 46 (15.2%) fatal cases had seizure disorders. **Death (≥18 years of age)** n=4 of 137 (2.9%) fatal cases had seizure disorders.	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
	and Dominican Republic					
Chaves SS, Aragon D, Bennett N, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010-2011 influenza season: exploring disease severity by virus type and subtype. J Infect Dis. 2013;208(8):1305-14.[31]	Design: Population case series Period: October 2010–April 2011 Location: USA	Case definition: Patient hospitalized with community-acquired, laboratory-confirmed influenza virus infection, excluding pregnant women with influenza Viral testing: Direct or indirect fluorescent antibody staining, RIDT, RT-PCR, or viral culture	Seasonal influenza A and B (2010–2011) n=163 of 830 (19.6%) hospitalized pediatric cases infected with influenza A(H1N1), 252 (30.4%) with influenza A(H3N2), and 415 (50.0%) with influenza B n=761 of 2791 (27.3%) hospitalized adult cases infected with influenza A(H1N1), 1497 (53.6%) with influenza A(H3N2), and 533 (19.1%) with influenza B	n=3621 hospitalized cases (n=830 [22.9%] hospitalized pediatric cases and 2791 [77.1%] hospitalized adult cases), including 677 ICU or fatal cases (n=141 [20.8%] ICU or fatal pediatric cases and 536 [79.2%] ICU or fatal adult cases) Age group: Predominantly adults (subgroup reporting for hospitalization and ICU admission or death outcomes for children <18 years of age and adults ≥18 years of age) Age at hospitalization: n=830 of 3621 (22.9%) hospitalized cases <18 years of age	**Hospitalization (<18 years of age)** n=38 of 830 (4.6%) hospitalized cases had neuromuscular disorders and 49 of 792 (6.2%) had developmental delay without neuromuscular disorders (n=351 [42.3%] hospitalized cases had at least one underlying medical condition). **ICU admission or death (<18 years of age)** n=16 of 141 (11.3%) ICU or fatal cases had neuromuscular disorders and 10 of 125 (8.0%) had developmental delay without neuromuscular disorders (n=72 [51.1%] ICU or fatal cases had at least one underlying medical condition). Neuromuscular disorders were significantly more common among hospitalized children with severe influenza (ICU admission or in-hospital death) than children with non-severe influenza (11.3% vs. 3.2%, p<0.0001), but not developmental delay without neuromuscular disorders (8.0% vs. 5.8%, p=0.36).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Hospitalization (≥18 years of age) n=211 of 2791 (7.6%) hospitalized cases had neuromuscular disorders (n=2386 [85.5%] hospitalized cases had at least one underlying medical condition). **ICU admission or death (≥18 years of age)** n=53 of 536 (9.9%) ICU or fatal cases had neuromuscular disorders (n=466 [86.9%] ICU or fatal cases had at least one underlying medical condition). Neuromuscular disorders were significantly higher among hospitalized adults with severe influenza (ICU admission or in-hospital death) than adults with non-severe influenza (9.9% vs. 7.0%, p=0.02). Presence of neuromuscular disorders was a significant predictor of influenza severity (ICU admission or in-hospital death) among hospitalized children (aOR: 4.84, 95% CI: 2.02–11.56, p=0.0004) and adults (aOR: 1.68, 95% CI: 1.11–2.52, p=0.01).	
Chaves SS, Perez A, Farley MM, et al. The burden of influenza	Design: Population case series	Case definition: Patient (<12 months of age) hospitalized with	Seasonal influenza A and B and pandemic	n=3157 hospitalized cases Age group: Children	**Hospitalization** n=104 of 3157 (3.3%) hospitalized cases had	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
hospitalizations in infants from 2003 to 2012, United States. Pediatr Infect Dis J. 2014;33(9):912-9.[32]	Period: 2003–2012 Location: USA	laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR, viral culture, direct or indirect fluorescent antibody assay, or RIDT	influenza A(H1N1)pdm09 (2003–2004 through 2011–2012) n=2593 of 3157 (82.1%) hospitalized cases infected with influenza A and 347 (11.0%) with influenza B		neurologic and neuromuscular disorder (n=796 [25.2%] hospitalized cases had at least one high-risk condition). The prevalence of neurologic and neuromuscular disorders increased with age (p<0.0001). **ICU admission** Neurologic and neuromuscular disorder was a significant risk factor associated with admission of infants <12 months to the ICU during hospitalization (aOR: 2.99, 95% CI: 1.87–4.78, p<0.001).	
Chen WH, Lu CY, Shao PL, et al. Risk factors of severe novel influenza A (H1N1) infections in hospitalized children. J Formos Med Assoc. 2012;111(8):421-6.[33]	Design: Clinical case series (single centre) Period: July–December 2009 Location: Taiwan	Case definition: Patient (children; age range not defined) hospitalized with laboratory-confirmed influenza virus infection Viral testing: Positive influenza A virus isolation or RIDT followed by rtRT-PCR for influenza A(H1N1)pdm09	Pandemic influenza A(H1N1)pdm09	n=61 hospitalized cases (n=14 [23.0%] ICU and/or fatal cases) Age group: Predominantly children Median age at hospitalization: 7.3 years (range: 0.1–18.1 years) Median age at ICU admission or death: 8.1 years (range: 0.6–18.1 years)	**Hospitalization** n=4 of 61 (6.6%) hospitalized cases had a CNS anomaly, including neurocognitive, neuromuscular, or seizure disorders (n=25 [41.0%] hospitalized cases had any comorbidities). **ICU admission and/or death** n=2 of 14 (14.3%) ICU and/or fatal cases had a CNS anomaly, including neurocognitive, neuromuscular, or seizure disorders (n=8 [57.1%] ICU and/or fatal cases had any comorbidities). CNS anomaly	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					(neurocognitive, neuromuscular, or seizure disorders) was not associated with ICU admission and/or death among hospitalized cases (p=0.47).	
Chien YS, Su CP, Tsai HT, et al. Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan. J Infect. 2010;60(2):168-74.(34)	Design: Population case series Period: July–August 2009 Location: Taiwan	Case definition: Patient hospitalized with pneumonia and laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=96 hospitalized cases with pneumonia Age group: Mixture of children and adults Median age at hospitalization: 18 years (range: 0.7–73 years; 51% of hospitalized cases with pneumonia were adults)	**Hospitalization with pneumonia** n=12 of 96 (12.5%) hospitalized cases had neurodevelopmental diseases (n=54 [56.3%] hospitalized cases had any pre-existing medical condition). **Hospitalization with pneumonia and respiratory failure** n=2 of 22 (9.1%) hospitalized cases with respiratory failure had neurodevelopmental diseases (n=15 [68.2%] hospitalized cases with respiratory failure had any pre-existing medical condition). Neurodevelopmental disease was not associated with severe complicated influenza infection (i.e., pneumonia and respiratory failure) among hospitalized cases.	Level III n/a
Chiu SS, Chan KH, Wong WH, Chan EL, Peiris JS. Age-matched comparison of children hospitalized for 2009	Design: Case-control (single centre) Period: July–	Case definition: Patient (<18 years of age) hospitalized with laboratory-confirmed influenza virus infection	Pandemic influenza A(H1N1)pdm09 Seasonal	n=99 hospitalized pandemic cases, 99 age-matched hospitalized seasonal A(H1N1) controls, 99 age-matched hospitalized	**Hospitalization (pandemic)** n=10 of 99 (10.1%) hospitalized pandemic cases had underlying neurologic condition (n=40 [40.4%]	Level II-2 Good

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
pandemic H1N1 influenza with those hospitalized for seasonal H1N1 and H3N2. PLoS One. 2011;6(7):e21837.[35]	September 2009 (pandemic cases and concurrent seasonal controls; NR for historical controls) Location: China (Hong Kong)	Control definition: Age-matched patient hospitalized for seasonal influenza A(H1N1) and A(H3N2) in previous influenza seasons or in the period concurrent with pandemic influenza Viral testing: Direct antigen detection and viral culture, with further subtype-specific RT-PCR assay	influenza A n=33 of 37 (89.2%) concurrent hospitalized seasonal controls infected with influenza A(H3N2) and 4 (10.8%) with influenza B	A(H3N2) controls, and 37 concurrent hospitalized seasonal influenza controls Age group: Children Median age at hospitalization: 5.7 years (range: 0.4–17.4 years) for pandemic cases and 2.7 years (range: <0.1–11 years) for concurrent seasonal influenza controls	hospitalized pandemic cases had at least one underlying condition). **Hospitalization (seasonal)** n=5 of 99 (5.1%) age-matched hospitalized seasonal influenza A(H1N1) controls had underlying neurologic condition (n=23 [23.2%] age-matched hospitalized seasonal influenza A(H1N1) controls had at least one underlying condition). n=7 of 99 (7.1%) age-matched hospitalized seasonal influenza A(H3N2) controls had underlying neurologic condition (n=23 [23.2%] age-matched hospitalized seasonal influenza A(H3N2) controls had at least one underlying condition). n=2 of 37 (5.4%) concurrent hospitalized seasonal influenza controls had underlying neurologic condition (n=7 [18.9%] concurrent hospitalized seasonal influenza controls had at least one underlying condition). **Pandemic vs. seasonal (hospitalization)** Patients hospitalized for pandemic influenza	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					A(H1N1)pdm09 were not more likely to have underlying neurologic condition compared to age-matched patients hospitalized for seasonal influenza A(H1N1) or A(H3N2), seasonal influenza in the period concurrent with pandemic influenza, or all seasonal influenza.	
Chong CY, Tan NW, Menon A, Thoon KC, Tee NW, Fu S. Risk Factors for Complicated Influenza A (H1N1) 2009 Disease in Children. Ann Acad Med Singapore. 2013;42(5):232-6.[36]	Design: Case-control (single centre) Period: May–July 2009 (cases) and May–June 2009 (controls) Location: Singapore	Case definition: Patient (<17 years of age) hospitalized with complicated illness (invasive bacterial infection, neurologic symptoms, severe dehydration, exacerbation of chronic disease and any disease requiring admission to hospital) and laboratory-confirmed influenza virus infection Control definition: Patient (<17 years of age) hospitalized for isolation purposes with only upper respiratory tract infection and laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=48 hospitalized cases with complicated illness and 95 controls hospitalized for isolation purposes Age group: Children Median age at hospitalization: 6.8 years (range: 0.2–16 years) for cases with complicated illness and 10.3 years (range: 0.5–16.9 years) for controls hospitalized for isolation purposes	**Hospitalization** n=2 of 48 (4.2%) hospitalized cases with complicated illness had neurologic disorders compared to 0 of 95 (0%) controls hospitalized for isolation purposes (n=18 [37.5%] hospitalized cases with complicated illness had at least one significant comorbidity). Univariate/multivariate analysis for neurologic disorders was not performed/NR.	Level II-2 Fair
Çiftçi E, Tuygun N, Özdemir H, et al. Clinical and epidemiological	Design: Clinical case series (multi-centre)	Case definition: Patient (<18 years of age) hospitalized with ILI and laboratory-confirmed	Pandemic influenza A(H1N1)pdm09	n=821 hospitalized cases (n=35 [4.3%] fatal cases) Age group: Children	**Hospitalization** n=106 of 821 (12.9%) hospitalized cases had chronic neurological disease	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
features of Turkish children with 2009 pandemic influenza A (H1N1) infection: experience from multiple tertiary paediatric centres in Turkey. Scand J Infect Dis. 2011;43(11-12):923-9.[37]	Period: July 2009–February 2010 Location: Turkey	influenza virus infection Viral testing: RT-PCR		Median age at hospitalization: 3 years (range: <0.1–18 years)	(n=376 [45.8%] hospitalized cases had at least one pre-existing condition). Rate of ICU admission (p<0.001), rate of mechanical ventilation (p<0.001), and duration of hospital-stay (p=0.022) were significantly higher in patients with chronic neurological disease, but not length of ICU stay. **Death** n=9 of 35 (25.7%) fatal cases had chronic neurological disease (n=26 [74.3%] fatal cases had at least one pre-existing condition). Mortality rate was significantly higher in patients with chronic neurological disease (p=0.034).	
Coffin SE, Zaoutis TE, Rosenquist AB, et al. Incidence, complications, and risk factors for prolonged stay in children hospitalized with community-acquired influenza. Pediatrics. 2007;119(4):740-8.[38] *(Supplemented with additional details from Keren R, et al. JAMA.*	Design: Clinical case series (single centre) Period: July 2000–June 2004 Location: USA	Case definition: Patient (≤21 years of age) hospitalized with community-acquired, laboratory-confirmed influenza virus infection (ICD-9 codes: 487, 487.0, 487.1, and 487.8) Viral testing: Enzyme immunoassay, with 7-valent DFA staining performed on enzyme immunoassay-negative	Seasonal influenza A and B (2000–2001 through 2003–2004) n=591 of 745 (79.3%) hospitalized cases infected with influenza A and 154 (20.7%) with influenza B	n=745 hospitalized cases Age group: Predominantly children Median age at hospitalization: 1.8 years (n=718 [96.4%] hospitalized cases <18 years of age)	**Hospitalization** n=89 of 745 (11.9%) hospitalized cases had neurologic and neuromuscular disease, including unspecified seizure disorders (n=37), cerebral palsy (n=36), hydrocephalus/cerebrospinal fluid shunt (n=27), febrile seizures (n=14), hypotonia (n=6), spinal muscular atrophy (n=4), hypoxic ischemic encephalopathy	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
2005;294(17):2188-94.(155) [Frequency of specific neurologic and neuromuscular diseases and association with respiratory failure outcome] and Newland JG, et al. J Pediatr. 2007;150(3):306-10.(158) [Association with influenza-related neurological complication outcome])		samples, followed by viral culture performed on enzyme immunoassay- and DFA-negative samples Risk group definition: ACIP			(n=3), muscular dystrophies (n=3), arthrogryposis (n=2), and 11 other listed conditions (n=1 for each condition) (n=363 [48.7%] hospitalized cases had any ACIP-defined high-risk chronic medical condition). Neurologic and neuromuscular disease was significantly associated with prolonged length of hospital stay (age-aOR: 5.7, 95% CI: 3.3–9.7), respiratory failure (aOR: 6.0, 95% CI: 2.7–13.5), and influenza-related neurological complications (age-aOR: 5.6, 95% CI: 3.2–9.6; n=842 hospitalized cases, including 97 excluded in Coffin et al. study).	
Cox CM, Blanton L, Dhara R, Brammer L, Finelli L. 2009 Pandemic influenza A (H1N1) deaths among children--United States, 2009-2010. Clin Infect Dis. 2011;52 Suppl 1:S69-74.(39) *(Dataset overlaps with Blanton L, et al. Pediatrics. 2012;130(3):390-6.(22) [Pandemic deaths])*	Design: Population case series Period: October 2007–April 2009 (fatal seasonal cases) and April 2009–January 2010 (fatal pandemic cases) Location: USA	Case definition: Death associated with laboratory-confirmed influenza virus infection in patients <18 years of age Viral testing: RT-PCR and fluorescent antibody testing for pandemic cases (n=45 of 317 [14.2%] cases with undetermined subtype classified as probable pandemic influenza A[H1N1]pdm09) and RIDT, viral isolation, enzyme immunoassay, fluorescent antibody	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2007–2008 and 2008–2009)	n=317 fatal pandemic cases (n=301 [95.0%] fatal pandemic cases with available information on underlying health status) and 155 fatal seasonal cases (n=146 [94.2%] fatal seasonal cases with available information on underlying health status) Age group: Children Median age at death: 9.4 years (range: 0–17 years) for pandemic cases and 6.2 years (range: 0–17 years) for seasonal cases	**Death (pandemic)** n=135 of 301 (44.9%) fatal pandemic cases had neurological disorders, including neurodevelopmental disorder (n=124), seizure disorder (n=67), and neuromuscular disorder (n=12). Neurodevelopmental disorders include cerebral palsy, moderate/severe developmental delay, congenital neurologic disorders, and other chronic nervous system disorders. Neuromuscular disorders include muscular dystrophy, spinal muscular atrophy, and	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		staining, immunohistochemical staining, or RT-PCR for seasonal cases Risk group definition: ACIP			mitochondrial disorders (n=205 [68.1%] fatal pandemic cases had an ACIP-defined high-risk chronic medical condition). **Death (seasonal)** n=35 of 146 (24.0%) fatal seasonal cases had neurological disorders, including neurodevelopmental disorder (n=30), seizure disorder (n=17), and neuromuscular disorder (n=3) (n=67 [45.9%] fatal seasonal cases had an ACIP-defined high-risk chronic medical condition). **Pandemic vs. seasonal (death)** A significant difference was found between pandemic influenza A(H1N1)pdm09 and seasonal influenza A and B cases for the proportion of deaths with neurodevelopmental disorder (p=0.02), but not any neurological disorder (p=0.05), seizure disorder (p=0.26) or neuromuscular disorders (p=0.67).	
Custodio HT, Gayle MO, Bailey CS, Wludyka PS, Rathore MH. Comparison of ICU and non-ICU patients infected with the 2009 H1N1 influenza virus in a	Design: Clinical case series (single centre) Period: April–December 2009	Case definition: Patient (≤21 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR (n=113 of 119 [95.0%])	Pandemic influenza A(H1N1)pdm09	n=119 hospitalized cases (n=25 [21.0%] ICU cases) Age group: Predominantly children Median age at hospitalization: 6 years	**Hospitalization** n=21 of 119 (17.6%) hospitalized cases had a neurodevelopmental condition (n=85 [71.4%] hospitalized cases had a chronic medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Florida Children's hospital between April and December 2009. Eastern Journal of Medicine. 2011;16(3):188.(40)	Location: USA	or viral culture (n=6 [5.0%]) (n=104 [87.4%] hospitalized cases with presumed and 15 [12.6%] with confirmed pandemic influenza A[H1N1]pdm09 infection)		(range: 0.04–20 years) Median age at ICU admission: 8 years (range: 0.5–20 years)	**ICU admission** n=8 of 25 (32.0%) ICU cases had neurodevelopmental a condition. Neurodevelopmental condition was significantly associated with ICU admission among hospitalized cases (p=0.034).	
Da Dalt L, Chillemi C, Cavicchiolo ME, et al. Pandemic influenza A (H1N1v) infection in pediatric population: a multicenter study in a north-east area of Italy. Ital J Pediatr. 2011;37:24.(41)	Design: Population case series Period: October 2009–January 2010 Location: Italy (Northeast area)	Case definition: Patient (<15 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR, with some samples sequenced	Pandemic influenza A(H1N1)pdm09	n=200 hospitalized cases (n=11 [5.5%] ICU cases) Age group: Children Median age at hospitalization: 4.15 years (range: 0–15 years) Median age at ICU admission: 3.8 years (range: 2.4–4.6 years)	**Hospitalization** n=22 of 200 (11.0%) hospitalized cases had pre-existing neurological disease (n=79 [39.5%] hospitalized cases had pre-existing conditions). **ICU admission** n=5 of 11 (45.5%) ICU cases admitted to ICU had pre-existing neurological disease (n=10 [90.9%] ICU cases had pre-existing condition). Pre-existing neurological disease was a significant risk factor for admission to ICU (aOR: 7.82, 95% CI: 1.15–53.34).	Level III n/a
Dalziel SR, Thompson JM, Macias CG, et al. Predictors of severe H1N1 infection in children presenting within Pediatric Emergency Research Networks (PERN): retrospective case-	Design: Case-control (multi-centre) Period: April–December 2009 Location: 12	Case definition: Patient (<16 years of age) presented to the ED with ILI and laboratory-confirmed influenza virus infection and subsequently died or admitted to ICU	Pandemic influenza A(H1N1)pdm09	n=265 cases with severe outcomes (admission to ICU or death), 265 random controls, and 265 age-matched controls Age group: Children Mean age of cases (SD): 6.6	**ICU admission or death** n=72 of 265 (27.2%) cases had cerebral palsy/developmental delay (n=193 [72.8%] hospitalized cases had pre-existing comorbidities). A history of cerebral	Level II-2 Fair

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
control study. BMJ. 2013;347:f4836.(42)	countries as part of Pediatric Emergency Research Networks	Control definition: Patient (<16 years of age) presented to the same ED as cases without development of severe outcomes and selected independently of hospital admission or laboratory testing (one random control and one age-matched control for each case) Presentation: Fever (≥37.8°C) and either cough or sore throat Viral testing: RT-PCR or viral culture for cases		(4.7) years (age of matched controls were similar to cases; age of random controls were on average 14 months younger)	palsy/developmental delay was significantly associated with severe outcomes (death or admission to ICU) in children presenting with ILI (aOR: 10.2, 95% CI: 2.0–51.4 [random controls]; aOR: 65.9, 95% CI: 8.6–506 [age-matched controls]).	
Damak H, Chtara K, Bahloul M, et al. Clinical features, complications and mortality in critically ill patients with 2009 influenza A(H1N1) in Sfax, Tunisia. Influenza Other Respir Viruses. 2011;5(4):230-40.(43)	Design: Clinical case series (single centre) Period: November 2009–January 2010 Location: Tunisia	Case definition: Patient admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=32 ICU cases Age group: Predominantly adults Mean age at ICU admission (SD): 36.1 (20.7) years (range: 4–72 years; n=8 of 32 [25.0%] ICU cases ≤20 years of age)	**ICU admission** n=6 of 32 (18.8%) ICU cases had neurological or neuromuscular comorbidity, including epilepsy (n=2), ischemic stroke (n=1), cerebral palsy (n=2), and myasthenia (n=1) (n=21 [65.6%] ICU cases had comorbidities).	Level III n/a
Dawood FS, Fiore A, Kamimoto L, et al. Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008. J Pediatr. 2010;157(5):808-14.(44)	Design: Population case series Period: 2003–2008 (October–April of each influenza	Case definition: Patient (<18 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: Rapid antigen test (62–73%), direct or indirect	Seasonal influenza A and B (2003–2004 through 2007–2008) n=3525 of 4015 (87.8%) hospitalized	n=4015 hospitalized cases (n=2709 [67.5%] hospitalized cases with information on underlying developmental delay, febrile seizures, and neuromuscular disorder for influenza seasons 2004–2005 through 2007–2008)	**Hospitalization** n=191 of 2709 (7.1%) hospitalized cases had underlying developmental delay, 39 (1.4%) had febrile seizures, and 112 (4.1%) had a neuromuscular disorder (n=1335 [49.3%] hospitalized cases had one	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
	season) Location: USA	fluorescent antibody staining (14–27%), viral culture (10–16%), or RT-PCR (1–5%) Risk group definition: ACIP	cases with typed influenza viruses: n=2980 of 3525 (84.5%) infected with influenza A and 545 (15.5%) with influenza B	Age group: Children	or more underlying medical conditions). n=180 of 4015 (4.5%) hospitalized cases had underlying seizure disorder (n=1894 [47.2%] hospitalized cases had one or more underlying medical conditions).	
De Keyser J, Zwanikken C, Boon M. Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. J Neurol Sci. 1998;159(1):51-3.[45]	Design: Self-controlled case series Period: November 1995–February 1996 Location: Netherlands	Case definition: Patient with primary progressive MS (progressive course from onset without superimposed exacerbations) or relapsing MS (relapsing-remitting form with or without secondary progression as well as the progressive-relapsing form) Vaccination status: Questionnaire Viral testing: None; self-reported influenza illness (abrupt onset of fever [≥38°C] with coryza, cough, or sore throat, and body aches) without laboratory-confirmed influenza infection	Seasonal influenza vaccine (1995–1996)	n=233 MS patients (n=53 [22.7%] patients with primary progressive MS without superimposed exacerbations and 180 [77.3%] patients with relapsing MS) Age group: Predominantly adults (assumed; age range NR) Mean age of MS patients with primary progressive MS (SD): 55 (9) years Mean age of MS patients with relapsing MS (SD): 44 (11) years	**Post-vaccination (exacerbation)** MS patients with primary progressive MS did not report clinically relevant exacerbations within six weeks following influenza illness or seasonal influenza vaccination. n=12 of 36 (33.3%) MS patients with relapsing MS experienced exacerbations within six weeks following influenza illness, but only 4 of 80 (5.0%) experienced exacerbations following seasonal influenza vaccination (p<0.0001). Exacerbation rate following influenza illness remained significantly higher than vaccination regardless of disability status (not restricted to wheelchair: p=0.005; essentially restricted to wheelchair: p=0.001).	Level III n/a
del Rosal T, Baquero-Artigao F, Calvo C, et	Design: Population	Case definition: Patient (≤14 years of age)	Pandemic influenza	n=517 hospitalized cases (n=51 [9.9%] ICU cases and	**Hospitalization** n=30 of 517 (5.8%)	Level III

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
al. Pandemic H1N1 influenza-associated hospitalizations in children in Madrid, Spain. Influenza Other Respir Viruses. 2011;5(6):e544-51.(46)	case series Period: May–November 2009 Location: Spain (Madrid)	hospitalized with laboratory-confirmed influenza virus infection Risk group definition: Spanish Association of Pediatrics Viral testing: RT-PCR	A(H1N1)pdm09	5 [1.0%] fatal cases) Age group: Children Mean age at hospitalization (SD): 4.7 (3.9) years Mean age at ICU admission (SD): 4.4 (3.7) years	hospitalized cases had underlying neurological or neuromuscular disorders (n=142 [27.5%] hospitalized cases had any underlying health condition). **ICU admission** n=8 of 51 (15.7%) ICU cases had underlying neurological or neuromuscular disorders (n=29 [56.9%] ICU cases had any underlying health condition). Underlying neurological or neuromuscular disorder was significantly associated with ICU admission (aOR: 4.2, 95% CI: 1.5–11.3, p=0.006). **Death** n=3 of 5 (60.0%) fatal cases had underlying health conditions with possible neurological impairment, including malignant peripheral nerve sheath tumor with cerebral metastasis, Edwards' syndrome, and severe encephalopathy with cerebral palsy and seizure disorder (n=5 [100.0%] fatal cases had any underlying health condition).	n/a
Desmoulins C, Michard-Lenoir AP, Naud J, Claudet I, Nouyrigat V, Chéron G. [Clinical features and	Design: Clinical case series (multi-centre)	Case definition: Patient presented to the ED with ILI and laboratory-confirmed influenza virus infection	Pandemic influenza A(H1N1)pdm09	n=466 ED cases Age group: Children Median age at ED	**ED presentation** n=20 of 466 (4.3%) ED cases had chronic neurologic disease, including severe epilepsy and myopathy, and	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
outcome of 2009 H1N1 influenza in the pediatric setting. Multicenter prospective study in the ED]. Arch Pediatr. 2011;18(5):505-11.(47)	Period: October–December 2009 Location: France	Viral testing: RT-PCR		presentation: 4 years (range: <0.1–17 years)	13 (2.8%) had encephalopathy (n=208 [44.6%] ED cases had a risk factor).	
Dhanoa A, Fang NC, Hassan SS, Kaniappan P, Rajasekaram G. Epidemiology and clinical characteristics of hospitalized patients with pandemic influenza A (H1N1) 2009 infections: the effects of bacterial coinfection. Virol J. 2011;8:501.(48)	Design: Clinical case series (single centre) Period: September 2009–May 2010 Location: Malaysia	Case definition: Patient (≤21 years of age) hospitalized with ILI and laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=50 hospitalized cases Age group: Mixture of children and adults Median age at hospitalization: 20.3 years (range: 0.6–82 years; n=23 of 50 [46.0%] hospitalized cases ≤15 years of age)	**Hospitalization** n=1 of 50 (2.0%) hospitalized cases had stroke (n=24 [48.0%] hospitalized cases had a comorbidity).	Level III n/a
Eriksson CO, Graham DA, Uyeki TM, Randolph AG. Risk factors for mechanical ventilation in U.S. children hospitalized with seasonal influenza and 2009 pandemic influenza A. Pediatr Crit Care Med. 2012;13(6):625-31.(49)	Design: Population case series Period: July 2006–March 2009 (seasonal) and June–December 2009 Location: USA	Case definition: Patient (<18 years of age) hospitalized with influenza virus infection (ICD-9-CM code: 487 or 488.1; 488.1 corresponds to laboratory-confirmed pandemic influenza) Viral testing: Specific methods NR; influenza virus infection during the pandemic season presumed to be A(H1N1)pdm09 Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2006–2007 through 2008–2009)	n=9837 hospitalized pandemic cases and 10,173 hospitalized seasonal cases (n=940 of 10,173 [9.2%] mechanically ventilated seasonal cases) Age group: Children Median age at hospitalization: 5.0 years (IQR: 1.4–9.5 years) for pandemic cases and 1.9 years (IQR: 0.5–6.3 years) for seasonal cases	**Hospitalization (pandemic)** n=1385 of 9837 (14.1%) hospitalized pandemic cases had neurological disease (n=5863 [59.6%] hospitalized pandemic cases had an ACIP-defined condition). **Hospitalization (seasonal)** n=1425 of 10,173 (14.0%) hospitalized seasonal cases had neurological disease (n=5045 [49.6%] hospitalized seasonal cases had an ACIP-defined condition). **Pandemic vs. seasonal (hospitalization)** The proportion with neurological disease was not significantly different	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					between hospitalized pandemic influenza A(H1N1)pdm09 and seasonal influenza A and B cases (14.1% vs. 14.0%, p=0.88). **Mechanical ventilation (seasonal)** n=334 of 940 (35.5%) mechanically ventilated seasonal cases had neurological disease (n=643 [68.4%] mechanically ventilated seasonal cases had an ACIP-defined condition). Neurological disease was significantly associated with mechanical ventilation among hospitalized seasonal cases in univariate (OR: 4.11, 95% CI: 3.55–4.77, p<0.001) and multivariate (aOR: 4.05, 95% CI: 3.79–4.33, p<0.001) analyses.	
Farias JA, Fernández A, Monteverde E, et al. Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina. Intensive Care Med. 2010;36(6):1015-22.(50)	Design: Population case-series Period: June–July 2009 Location: Argentina	Case definition: Patient (children; age range not defined) admitted to ICU with acute respiratory failure and required invasive or non-invasive mechanical ventilation, fraction of inspired oxygen on face mask ≥60%, and/or administration of inotropes or vasopressors and with laboratory-confirmed	Pandemic influenza A(H1N1)pdm09	n=147 ICU cases (n=57 [38.8%] fatal ICU cases) Age group: Children Median age at ICU admission: 0.8 years (IQR: 0.3–4.9 years)	**ICU admission** n=24 of 147 (16.3%) ICU cases had a chronic neuromuscular condition (n=68 [46.3%] ICU cases had at least one complex chronic condition). **ICU death** n=12 of 57 (21.1%) fatal ICU cases had a chronic neuromuscular condition (n=34 [59.6%] fatal ICU cases had at least one	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		influenza virus infection Viral testing: rtRT-PCR			complex chronic condition). Chronic neuromuscular condition was not associated with death among ICU cases (p=0.21).	
Ferdinands JM, Olsho LE, Agan AA, et al. Effectiveness of influenza vaccine against life-threatening RT-PCR-confirmed influenza illness in US children, 2010-2012. J Infect Dis. 2014;210(5):674-83.(51)	Design: Case-control (multi-centre) Period: 2010–2011 and 2011–2012 Location: USA	Case definition: Patient (6 months–17 years of age) admitted to ICU with SARI and laboratory-confirmed influenza virus infection Presentation: Symptomatic for acute severe viral infection by at least one of the following: lower respiratory tract infection, shock requiring vasoactive agents, CNS dysfunction, or acute increase in respiratory support Control definition: Patient (6 months–17 years of age) admitted to ICU with SARI with negative laboratory test for influenza virus infection (ICU controls) or child without an influenza-associated hospitalization between September of the study year and the matched case's ICU admission date Cases and community	Seasonal influenza (2010–2011 and 2011–2012)	n=44 ICU cases, 174 ICU controls, and 93 community controls Age group: Children Median age of ICU cases: 4.3 years (IQR: 2.8–7.7 years) Median age of ICU controls: 3 years (IQR: 1.3–6.6 years) Median age of community controls: 4.5 years (IQR: 1.8–9.4 years)	**ICU admission** n=16 of 44 (36.4%) ICU cases had neuromuscular disease, excluding neuromuscular disease requiring chronic mechanical ventilator support through a mask or tracheostomy for neuromuscular weakness (55% of ICU cases had least one underlying chronic medical condition). Univariate/multivariate analysis for neuromuscular disease was not performed/NR.	Level II-2 Fair

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		controls matched by comorbidities and geographic region Viral testing: rtRT-PCR				
Feret V, Naud J, Harambat J, Malato L, Fleury H, Fayon M. [Viral epidemiology and clinical severity during the peak of the influenza A(H1N1) variant epidemic in febrile respiratory diseases of children]. Arch Pediatr. 2014;21(7):709-15.(52)	Design: Clinical case series (single centre) Period: November–December 2009 Location: France	Case definition: Patient (<15 years of age) hospitalized for febrile respiratory disease with laboratory-confirmed respiratory virus infection, including influenza Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=17 hospitalized cases with pandemic influenza A(H1N1) infection Age group: Children Median age at hospitalization: 1 year (range: <0.1–9 years)	**Hospitalization** n=2 of 17 (11.8%) hospitalized cases had epilepsy (n=8 [47.1%] hospitalized cases had a risk factor).	Level III n/a
Fowlkes AL, Arguin P, Biggerstaff MS, et al. Epidemiology of 2009 pandemic influenza A (H1N1) deaths in the United States, April-July 2009. Clin Infect Dis. 2011;52 Suppl 1:S60-8.(53)	Design: Population case series Period: April–July 2009 Location: USA	Case definition: Death associated with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09	n=377 fatal cases (n=324 [85.9%] fatal cases with available information on underlying medical conditions) Age group: Predominantly adults (subgroup reporting for death outcome for children <18 years of age and adults ≥18 years of age) Median age at death: 43 years (range: 0.2–85 years; n=48 of 327 [14.7%] fatal cases <18 years of age)	**Death** n=58 of 324 (18.1%) fatal cases had neurologic disorder/developmental delay, including neurodevelopmental disorder (n=41), neuromuscular disorder (n=6), and seizure disorder (n=24) (n=253 [78.1%] fatal cases had at least one underlying medical condition). **Death (<18 years of age)** n=26 of 48 (54.2%) fatal cases had neurologic disorder/developmental delay (n=22 [84.6%] with >1 neurologic condition), including neurodevelopmental disorder (n=25), neuromuscular disorder (n=3), and seizure	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					disorder (n=12) (n=33 [68.8%] fatal cases had at least one underlying medical condition). **Death (≥18 years of age)** n=32 of 276 (11.6%) fatal cases (≥18 years of age) had neurologic disorder/developmental delay, including neurodevelopmental disorder (n=16), neuromuscular disorder (n=3), and seizure disorder (n=12) (n=220 [79.7%] fatal cases had at least one underlying medical condition).	
Garcia MN, Philpott DC, Murray KO, et al. Clinical predictors of disease severity during the 2009-2010 A(HIN1) influenza virus pandemic in a paediatric population. Epidemiol Infect. 2015;143(14):2939-49.(54)	Design: Clinical case series (single centre) Period: April 2009–June 2010 Location: USA	Case definition: Patient (≤18 years of age) presented to the ED with laboratory-confirmed influenza virus infection and subsequently non-hospitalized, hospitalized without ICU admission, or hospitalized with ICU admission (hospitalization was defined as those admitted for ≥24 hours) Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=695 ED cases (n=263 [37.8%] hospitalized, non-ICU cases and 116 [16.7%] ICU cases) Age group: Children	**ED presentation** n=28 of 695 (4.0%) ED cases had developmental delay, 30 (4.3%) had neurocognitive disorder, 4 (0.6%) had neurological condition, 4 (0.6%) had neuromuscular disorder, and 27 (3.9%) had seizure disorder (n=259 [37.3%] ED cases had any prior health condition). **Hospitalization, non-ICU** n=9 of 263 (3.4%) hospitalized, non-ICU cases had developmental delay, 7 (2.7%) had neurocognitive disorder, 0 (0%) had neurological condition, 3 (1.1%) had neuromuscular disorder, and 10 (3.8%) had seizure disorder (n=178	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					[67.7%] hospitalized, non-ICU cases had any prior health condition). **ICU admission** n=12 of 116 (10.3%) ICU cases had developmental delay, 11 (9.5%) had neurocognitive disorder, 4 (3.4%) had neurological condition, 1 (0.9%) had neuromuscular disorder, and 14 (12.1%) had seizure disorder (n=81 [69.8%] ICU cases had any prior health condition). Seizure disorder was significantly associated with hospitalization in ED presentations with laboratory-confirmed influenza virus infection (aOR: 4.71, 95% CI: 2.11–10.52, p<0.001), but not developmental delay (aOR: 2.20, 95% CI: 0.99–4.87, p=0.051), neurocognitive disorder, neurological condition, or neuromuscular disorder.	
Garnacho-Montero J, Gutiérrez-Pizarraya A, Màrquez JA, et al. Epidemiology, clinical features, and prognosis of elderly adults with severe forms of influenza A (H1N1). J Am Geriatr Soc. 2013;61(3):350-6.[55]	Design: Population case-series Period: April 2009–July 2011 Location: Spain	Case definition: Patient (≥15 years of age) admitted to ICU with laboratory-confirmed influenza virus infection Presentation: Fever (≥38°C), cough, sore throat, myalgia, or ILI,	Pandemic influenza A(H1N1)pdm09	n=1120 ICU cases Age group: Predominantly adults Median age at ICU admission for patients <65 years of age: 44 years (IQR: 35–53 years)	**ICU admission** n=30 of 1120 (2.7%) ICU cases had neuromuscular disease (n=814 [72.7%] ICU cases had at least one underlying disease).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		and acute respiratory failure requiring ICU admission Viral testing: rtRT-PCR				
Gastañaduy AS, Bégué RE. Experience with pandemic 2009 H1N1 influenza in a large pediatric hospital. South Med J. 2012;105(4):192-8.(56)	Design: Clinical case-series (single centre) Period: April 2009–May 2010 Location: USA	Case definition: Patient (children; age range not defined) diagnosed with laboratory-confirmed influenza virus infection Viral testing: RIDT, with DFA staining performed on RIDT-negative samples; positive samples typed by rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=1463 medically-attended cases (n=155 [10.6%] hospitalized cases) Age group: Children Median age at hospitalization: 3.9 years (IQR: 1.0–9.4 years)	**Hospitalization** n=16 of 155 (10.3%) hospitalized cases had a neuromuscular disorder (n=98 [63.2%] hospitalized cases had at least one comorbidity).	Level III n/a
Gaüzère BA, Bussienne F, Bouchet B, et al. [Severe cases of A(H1N1)v2009 infection in Réunion Island in 2009 and 2010]. Bull Soc Pathol Exot. 2011;104(2):97-104.(57)	Design: Clinical case series Period: 2009 Location: Réunion Island	Case definition: Patient admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=13 ICU cases Age group: Predominantly adults Median age at ICU admission: 37 years (range: 17–69 years)	**ICU admission** n=2 of 13 (15.4%) ICU cases had an underlying neurologic disorder, including cerebral palsy and Huntington's chorea with epilepsy (n=11 [84.6%] ICU cases had at least one risk factor).	Level III n/a
Gilca R, De Serres G, Boulianne N, et al. Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. Influenza Other Respir Viruses. 2011;5(4):247-55.(58)	Design: Case-control (multi-centre) Period: May–July 2009 Location: Canada	Case definition: Patient hospitalized for ≥24 hours with laboratory-confirmed influenza virus infection Control definition: Medically-attended, non-hospitalized patient with laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=321 hospitalized cases (n=47 [14.6%] ICU cases and 15 [4.7%] fatal cases) and 395 non-hospitalized controls Age group: Mixture of children and adults Median age at hospitalization for cases: 24 years (n=145 of 321 [45.2%] hospitalized cases <20 years of age)	**Hospitalization** n=19 of 321 (5.9%) hospitalized cases had underlying neuromuscular condition, including cerebral palsy, muscular dystrophy, and developmental delay (n=186 [57.9%] hospitalized cases had at least one underlying medical condition). Underlying neuromuscular condition was significantly	Level II-2 n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					associated with hospitalization (aOR: 22.2, 95% CI: 2.6–186.0). **ICU admission** n=3 of 47 (6.4%) ICU cases had underlying neuromuscular condition (n=29 [61.7%] ICU cases had at least one underlying medical condition). **Death** n=1 of 15 (6.7%) fatal cases had underlying neuromuscular condition (n=9 [60.0%] fatal cases had at least one underlying medical condition). Underlying neuromuscular condition was not a significant risk factor for ICU admission or hospital mortality among hospitalized cases (aOR: 0.9, 95% CI: 0.2–3.6).	
Godoy P, Castilla J, Mayoral JM, et al. Smoking may increase the risk of hospitalization due to influenza. Eur J Public Health. 2016. [In press].[59]	Design: Case-control (multi-centre) Period: October 2010–April 2011 Location: Spain	Case definition: Patient (≥18 years of age) hospitalized due to influenza syndrome, ARI, septic shock or multiple organ failure for >24 hours with community-acquired, laboratory-confirmed influenza virus infection Control definition: Medically-attended, non-hospitalized patient with	Seasonal influenza (2010–2011)	n=471 hospitalized cases and 476 non-hospitalized controls Age group: Adults Mean age at hospitalization for cases (SD): 53.9 (15.9) years	**Hospitalization** n=12 of 471 (2.5%) cases had disabling neurological disease. Disabling neurological disease was not associated with hospitalization (p=0.10).	Level II-2 Fair

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		laboratory-confirmed influenza virus infection Cases and controls matched by age, province of residence, and date of hospital admission Viral testing: rtRT-PCR				
González-Candelas F, Astray J, Alonso J, et al. Sociodemographic factors and clinical conditions associated to hospitalization in influenza A (H1N1) 2009 virus infected patients in Spain, 2009–2010. PLoS One. 2012;7(3):e33139.(60)	Design: Case-control (multi-centre) Period: July 2009–February 2010 Location: Spain	Case definition: Patient hospitalized for ≥24 hours with community-acquired, laboratory-confirmed influenza virus infection Control definition: Medically-attended, non-hospitalized patient with laboratory-confirmed influenza virus infection Cases and controls matched by age, province of residence, and date of hospital admission Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=699 hospitalized cases and 703 non-hospitalized controls Age group: Predominantly adults Mean age at hospitalization for cases (SD): 37.8 (22.8) years (n=212 of 699 [30.3%] hospitalized cases <25 years of age)	**Hospitalization** n=31 of 699 (4.4%) hospitalized cases had disabling neurological disease (62.8% of hospitalized cases had at least one risk factor). Disabling neurological disease was significantly associated with hospitalization (aOR: 4.00, 95% CI: 1.24–12.99, p=0.02).	Level II-2 Fair
Grgic S, Skocibusic S, Celjuska-Tosev E, Nikolic J, Arapovic J, Kuzman I. Different features of influenza A H1N1pdm09 virus infection among adults in 2009/10 and 2010/11. J Infect Dev Ctries. 2016;10(2):155-	Design: Clinical case series (single centre) Period: July 2009–March 2010 (pandemic season) and	Case definition: Patient (≥18 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A(H1N1)pdm09 (2010–2011)	n=105 hospitalized pandemic cases and 123 hospitalized seasonal (post-pandemic) cases Age group: Adults Mean age at hospitalization (SD): 42.0 (27.0) years for pandemic cases and 49.0	**Hospitalization (pandemic)** n=5 of 105 (4.8%) hospitalized pandemic cases had neuromuscular disease (n=68 [64.8%] hospitalized pandemic cases had risk factors). **Hospitalization (seasonal)** n=17 of 123 (13.8%)	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
62.[61]	November 2010–March 2011 (post-pandemic season) Location: Croatia			(30.0) years for seasonal (post-pandemic) cases	hospitalized seasonal (post-pandemic) cases had neuromuscular disease (n=76 [61.8%] hospitalized post-pandemic cases had risk factors). **Pandemic vs. seasonal (hospitalization)** The proportion with neuromuscular disease was significantly different between hospitalized pandemic and seasonal (post-pandemic) influenza A(H1N1)pmd09 cases (4.7% vs. 13.8%, p=0.02).	
Gubbels S, Krause TG, Bragstad K, Perner A, Mølbak K, Glismann S. Burden and characteristics of influenza A and B in Danish intensive care units during the 2009/10 and 2010/11 influenza seasons. Epidemiol Infect. 2013;141(4):767-75.[62]	Design: Population case series Period: November 2009–March 2010 (pandemic) and December 2010–April 2011 (seasonal) Location: Denmark	Case definition: Patient admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2010–2011) n=106 of 148 (71.6%) seasonal ICU cases infected with influenza A (n=91 [85.8%] subtyped: all influenza A[H1N1]pdm09) and 42 (28.4%) with influenza B (n=17 [40.5%] subtyped: n=9 [52.9%] Victoria lineage and 8 [47.1%]	n=96 pandemic ICU cases and 148 seasonal (post-pandemic) ICU cases Age group: Predominantly adults Mean age at ICU admission: 44 years (range: 3–80 years) for pandemic cases and 53 years (range: <0.1–83 years) for seasonal cases	**ICU admission (pandemic)** n=9 of 47 (19.1%) pandemic ICU cases had neurological disease (n=41 of 52 [78.8%] pandemic ICU cases had an underlying condition). **ICU admission (seasonal)** n=1 of 115 (0.9%) seasonal ICU cases had neurological disease (n=91 of 115 [79.1%] seasonal ICU cases had an underlying condition). **Pandemic vs. seasonal (ICU admission)** The proportion with neurological disease was significantly different between pandemic and seasonal influenza A ICU cases (19.1% vs. 0.9%, p<0.001).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
			Yamagata lineage)			
Hagerman A, Posfay-Barbe KM, Duppenthaler A, Heininger U, Berger C; PIGS Influenza Study Group. Clinical characteristics and outcomes in children hospitalised with pandemic influenza A/H1N1/09 virus infection – a nationwide survey by the Pediatric Infectious Diseases Group of Switzerland. Swiss Med Wkly. 2015;145:w14171.(63)	Design: Population case series Period: June 2009–January 2010 Location: Switzerland	Case definition: Patient (≤18 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=326 hospitalized cases Age group: Children Median age at hospitalization: 3.6 years (range: 0–18.3 years)	**Hospitalization** n=27 of 326 (8.3%) hospitalized cases had neurological disease (excluding n=2 with Down syndrome, grouped as genetic disease), including seizures/epilepsy (n=9) and recurrent febrile seizures (n=3) (n=126 [38.7%] hospitalized cases had underlying medical conditions).	Level III n/a
Heininger U, Baer G, Ryser AJ, Li Y. Comparative analysis of clinical characteristics of pandemic influenza A/H1N1 and seasonal influenza a infections in hospitalized children. Pediatr Infect Dis J. 2013;32(3):293-6.(64)	Design: Population case series Period: September 2007–March 2009 (seasonal) and April 2009–March 2010 (pandemic) Location: Switzerland	Case definition: Patient (<18 years of age) hospitalized with community-acquired, laboratory-confirmed influenza virus infection Viral testing: RT-PCR (seasonal influenza A not subtyped/NR)	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A (2007–2008 and 2008–2009)	n=55 hospitalized pandemic cases and 79 hospitalized seasonal cases Age group: Children Median age at hospitalization: 2.5 years (IQR: 0.81–8.17 years; range: 0.07–15.5 years) for pandemic cases and 1.5 years (IQR: 0.67–6.72 years; range: 0.04–17.5 years) for seasonal cases	**Hospitalization (pandemic)** n=2 of 55 (3.6%) hospitalized pandemic cases had neurologic comorbidities (n=14 [25.5%] hospitalized pandemic cases had any comorbidity). **Hospitalization (seasonal)** n=8 of 79 (10.1%) hospitalized seasonal cases had neurologic comorbidities (n=26 [32.9%] hospitalized seasonal cases had an underlying comorbidity). **Pandemic vs. seasonal (hospitalization)** The proportion with neurologic comorbidities was not significantly different	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					between hospitalized pandemic influenza A(H1N1)pdm09 and seasonal influenza A cases (3.6% vs. 10.1%, p>0.05).	
Hlavinkova L, Kristufkova Z, Mikas J. Risk factors for severe outcome of cases with pandemic influenza A(H1N1)pdm09. Bratisl Lek Listy. 2015;116(6):389-93.(65)	Design: Population case series Period: May–December 2009 Location: Slovakia	Case definition: Patient with clinical symptoms of influenza and laboratory-confirmed influenza virus infection (a severe case was defined as those admitted to ICU, developed pneumonia, and/or died) Viral testing: RT-PCR or rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=1014 cases (n=57 [5.6%] severe cases) Age group: Mixture of children and adults Median age of severe cases: 35 years	**ICU admission and/or death** n=1 of 57 (1.8%) severe cases had neuromuscular disease (n=37 [64.9%] severe cases had at least one risk factor). Neuromuscular disease was not associated with severe outcome (admission to ICU, pneumonia development, and/or death, p>0.05).	Level III n/a
Hon KL, Leung E, Tang J, et al. Premorbid factors and outcome associated with respiratory virus infections in a pediatric intensive care unit. Pediatr Pulmonol. 2008;43(3):275-80.(66)	Design: Clinical case series (single centre) Period: January 2003–April 2007 Location: China (Hong Kong)	Case definition: Patient (children; age range not defined) admitted to ICU with laboratory-confirmed respiratory virus infection, including influenza Viral testing: DFA test, RT-PCR, viral culture with neutralization studies, or other (e.g., complement fixation test)	Seasonal influenza A and B n=10 of 13 (76.9%) ICU cases infected with influenza A and 3 (23.1%) with influenza B	n=13 ICU cases Age group: Children Median age at ICU admission: 4.8 years (range: 1.6–9.1 years)	**ICU admission** n=2 of 13 (15.4%) ICU cases had neurodevelopmental conditions (mental retardation, cerebral palsy, neuromuscular disease) and 1 (7.7%) had seizure disorder.	Level III n/a
Hong KW, Cheong HJ, Choi WS, et al. Clinical courses and outcomes of hospitalized adult patients with seasonal influenza in Korea, 2011–2012: Hospital-based Influenza Morbidity & Mortality	Design: Clinical case series (multi-centre) Period: October 2011–May 2012	Case definition: Patient (≥18 years of age) hospitalized with or without complication (other organ dysfunction beyond the upper respiratory tract, such as lower respiratory tract, heart, kidney, brain, and	Seasonal influenza A and B (2011–2012)	n=123 hospitalized cases, with 40 (32.5%) complicated cases (n=36 of 40 [90.0%] complicated cases had pneumonia) Age group: Adults Median age at	**Hospitalization** n=6 of 123 (4.9%) hospitalized cases had neuromuscular disease (n=75 [61.0%] hospitalized cases had any one underlying medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
(HIMM) surveillance. J Infect Chemother. 2014;20(1):9-14.(67)	Location: South Korea	muscles) and laboratory-confirmed influenza virus infection Viral testing: RIDT, rtRT-PCR, or viral culture		hospitalization: 74 years (IQR: 56–80 years) for complicated cases and 57 years (IQR: 40–73 years) for uncomplicated cases	Neuromuscular disease was significantly associated with complicated illness (p=0.02). Neuromuscular disease was not included in multivariate analysis due to small sample size (n=5 of 40 [12.5%] complicated cases had neuromuscular disease compared to 1 of 83 [1.2%] uncomplicated cases).	
Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med. 2009;361(20):1935-44.(68)	Design: Population case series Period: May–June 2009 Location: USA	Case definition: Patient hospitalized for ≥24 hours with ILI and laboratory-confirmed influenza virus infection Presentation: ILI: fever (≥37.8°C) and cough or sore throat Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=272 hospitalized cases (n=67 [24.6%] ICU or fatal cases and 19 [7.0%] fatal cases) Age group: Mixture of children and adults (subgroup reporting for hospitalization, ICU admission or death, and death outcomes for children <18 years of age and adults ≥18 years of age) Median age at hospitalization: 21 years (range: <0.1–86 years; n=122 of 272 [44.9%] hospitalized cases <18 years of age) Median age at ICU admission or death: 29 years (range: 1–86 years; n=24 of 67 ICU or fatal cases [35.8%] <18 years of age) Median age at death: 26 years (range: 1.3–57 years)	**Hospitalization** 14% of 272 hospitalized cases had neurocognitive (n=20), neuromuscular (n=19), or seizure disorders (n=18) (n=198 [50.7%] hospitalized cases had an underlying medical condition). **Hospitalization (<18 years of age)** 20% of 122 hospitalized cases had neurocognitive (n=14), neuromuscular (n=13), or seizure disorders (n=13) (n=73 [59.8%] hospitalized cases had an underlying medical condition). **Hospitalization (≥18 years of age)** 9% of 150 hospitalized cases had neurocognitive (n=6), neuromuscular (n=6), or seizure disorders (n=5) (n=125 [83.3%] hospitalized cases had an underlying medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					ICU admission or death n=12 of 67 (17.9%) ICU or fatal cases had underlying neurological diseases, including neurocognitive (n=9) or neuromuscular disorder (n=9) (n=45 [67.2%] ICU or fatal had an underlying medical condition). Neurological disorder was significantly associated with ICU admission or death among hospitalized cases ($p<0.05$). **Death** n=4 of 19 (21.1%) fatal cases had underlying neurologic disease (n=13 [68.4%] fatal cases had an underlying medical condition).	
Kappagoda C, Isaacs D, Mellis C, Peat J, De Silva L, O'Connell A. Critical influenza virus infection. J Paediatr Child Health. 2000;36(4):318-21.[69]	Design: Clinical case series (single centre) Period: 1977–1994 Location: Australia	Case definition: Patient (children; age range not defined) admitted to ICU or died with community-acquired, laboratory-confirmed influenza virus infection without laryngotracheobronchitis Viral testing: Immunofluorescence and/or viral culture	Seasonal influenza A and B	n=27 ICU or fatal cases Age group: Children Age range at ICU admission or death: <0.1–11.3 years	**ICU admission or death** n=5 of 27 (18.5%) ICU or fatal cases had neurologic conditions, including Down syndrome (n=2), cerebral palsy (n=2), and epilepsy (n=1) (n=16 [59.3%] ICU or fatal cases had underlying conditions).	Level III n/a
Kendirli T, Demirkol D, Yldzdas D, et al. Critically ill children with pandemic	Design: Clinical case series (multi-centre)	Case definition: Patient (1 month–18 years of age) admitted to ICU with laboratory-	Pandemic influenza A(H1N1)pdm09	n=83 ICU cases (n=25 [30.1%] fatal ICU cases) Age group: Children	**ICU admission** n=20 of 83 (24.1%) ICU cases had neurologic comorbidities, including	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
influenza (H1N1) in pediatric intensive care units in Turkey. Pediatric Critical Care Medicine. 2012;13(1):e11-7.[70]	Period: November–December 2009 Location: Turkey	confirmed influenza virus infection Presentation: Fever (≥37.8°C) and cough or sore throat Viral testing: rtRT-PCR		Median age at ICU admission: 3.5 years (0.2–17 years)	cerebral palsy, mental motor retardation, hydrocephaly, and epilepsy (n=16), muscle disease (n=2), and neurologic syndromes (n=2) (n=63 [75.9%] ICU cases had comorbidities). **ICU death** n=5 of 25 (20.0%) fatal cases had neurologic comorbidities (n=20 [80.0%] fatal cases had comorbidities). Neurology comorbidity was not associated with death among ICU cases (p=0.466).	
Khandaker G, Zurynski Y, Ridley G, et al. Clinical epidemiology and predictors of outcome in children hospitalised with influenza A(H1N1)pdm09 in 2009: a prospective national study. Influenza Other Respir Viruses. 2014;8(6):636-45.[71] *(Supplemented with additional details from* Khandaker G, et al. Neurology. 2012;79(14):1474-81.[156])	Design: Population case series Period: June–September 2009 Location: Australia	Case definition: Patient (<15 years of age) hospitalized with symptoms and/or signs consistent with influenza and laboratory-confirmed influenza virus infection Viral testing: RT-PCR (n=422 of 506 [83.4%]), RIDT (n=204 [40.3%]), DFA test (n=20 [3.9%]) and/or viral culture (n=12 [2.4%]), with 433 samples further subtyped	Pandemic influenza A(H1N1)pdm09	n=506 hospitalized cases (n=50 [9.9%] ICU cases and 5 [1.0%] fatal cases) Age group: Children Median age at hospitalization: 3.7 years (range: 0–14.9 years)	**Hospitalization** n=68 of 506 (13.4%) hospitalized cases had chronic neurological disease, including epilepsy (n=19), cerebral palsy/developmental delay (n=34), prior encephalopathy/syndrome of inappropriate secretion of antidiuretic hormone/hypoxic brain injury (n=6), and hydrocephalus/space-occupying lesion/spinal muscular atrophy (n=8) (n=248 [49.0%] hospitalized cases had pre-existing conditions). **ICU admission** Chronic neurological disease was a significant predictor of admission to ICU (aOR: 2.30, 95% CI: 1.14–4.61,	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					p=0.02). **Death** n=3 of 5 (60.0%) fatal cases had chronic neurological disease (n=4 [80.0%] fatal cases had pre-existing conditions).	
Koh MT, Eg KP, Loh SS. Hospitalised Malaysian children with pandemic (H1N1) 2009 influenza: clinical characteristics, risk factors for severe disease and comparison with the 2002-2007 seasonal influenza. Singapore Med J. 2016;57(2):81-6.(72)	Design: Clinical case series (single centre) Period: July 2009–June 2010 Location: Malaysia	Case definition: Patient (≤12 years of age) hospitalized with ILI and laboratory-confirmed influenza virus infection Presentation: ILI: sudden onset of fever (≥38°C) with respiratory tract symptoms and at least one of the following: muscle ache, headache, extreme fatigue or poor activity Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=77 hospitalized cases Age group: Children Age range at hospitalization: <0.1–11.7 years	**Hospitalization** n=9 of 77 (11.7%) hospitalized cases had neurological or neuromuscular disease (n=31 [40.3%] hospitalized cases had at least one comorbidity).	Level III n/a
Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA. 2009;302(17):1872-9.(73) *(Supplemented with additional details from Jouvet P, et al. Critical illness in children with influenza A/pH1N1*	Design: Population case series Period: April–August 2009 Location: Canada	Case definition: Patient admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: NR (n=162 of 168 [96.4%] cases with confirmed and 6 with probable influenza A[H1N1]pdm09)	Pandemic influenza A(H1N1)pdm09	n=168 ICU cases Age group: Predominantly adults (ICU admission); children (ICU admission; mechanical ventilation) Mean age at ICU admission (SD): 32.3 (21.4) years (n=50 of 168 [29.8%] ICU cases <18 years of age)	**ICU admission** n=26 of 168 (15.5%) ICU cases had neurological disease, including cerebrovascular disease (n=8), seizures (n=13), cerebral palsy (n=16), and other neurological disease (n=6) (n=165 [98.2%] ICU cases had any comorbidity and 51 [30.4%] had a major comorbidity). **ICU admission (<18 years of age)** n=13 of 57 (22.8%) ICU	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
2009 infection in Canada. Pediatr Crit Care Med. 2010;11(5):603-9.(154) [Subgroup reporting of ICU and mechanical ventilation cases for children <18 years of age]).					cases had neurological disease, including cerebral palsy (n=11), seizures (n=10), and other neurological disease (n=4) (n=40 [70.2%] ICU cases had any comorbidity). **Mechanical ventilation (<18 years of age)** Neurological disease was not significantly associated with mechanical ventilation among ICU cases (aHR: 3.07, 95% CI: 0.52–18.18).	
Kumar S, Havens PL, Chusid MJ, Willoughby RE Jr, Simpson P, Henrickson KJ. Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. Pediatr Infect Dis J. 2010;29(7):591-4.(74)	Design: Clinical case series (single centre) Period: April–August 2009 Location: USA	Case definition: Patient (children; age range not defined) hospitalized for ≥24 hours with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=75 hospitalized cases Age group: Predominantly children Median age at hospitalization: 5 years (range: 0.2–19.2 years)	**Hospitalization** n=7 of 75 (9.3%) hospitalized cases had underlying neuromuscular disorder, 6 (8.0%) had cognitive dysfunction, 5 (6.6%) had seizure disorder, and 1 (1.3%) had febrile seizures (n=56 [74.6%] hospitalized cases had at least one underlying medical condition).	Level III n/a
Kwong KL, Lung D, Wong SN, Que TL, Kwong NS. Influenza-related hospitalisations in children. J Paediatr Child Health. 2009;45(11):660-4.(75)	Design: Clinical case series (single centre) Period: January–June 2005 Location: China (Hong Kong)	Case definition: Patient (1 month–18 years of age) hospitalized with laboratory-confirmed influenza virus infection Presentation: Fever (>37.8°C), upper respiratory tract symptoms, and lower respiratory tract symptoms (afebrile patients tested at	Seasonal influenza A and B 93.5% of hospitalized cases infected with influenza A	n=123 hospitalized cases Age group: Children Median age at hospitalization: 3.5 years (range: <0.1–14 years)	**Hospitalization** n=11 of 123 (8.9%) hospitalized cases had a history of febrile seizures or other seizure disorders (n=18 [14.6%] hospitalized cases had underlying illness).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		discretion of attending pediatrician) Viral testing: RIDT and viral isolation				
Landau YE, Grisaru-Soen G, Reif S, Fattal-Valevski A. Pediatric Neurologic Complications Associated With Influenza A H1N1. Pediatr Neurol. 2011;44(1):47-51.(76)	Design: Clinical case series (single centre) Period: October 2009–January 2010 Location: Israel	Case definition: Patient (children; age range not defined) hospitalized with neurologic complications and laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=74 hospitalized with laboratory-confirmed influenza n=14 hospitalized cases with neurologic complications Age group: Children Mean age at hospitalization (SD): 5.4 (4.4) years (range: 0.2–16 years)	**Hospitalization (exacerbation)** n=7 of 11 (63.6%) hospitalized cases without a previous history of seizures presented with seizures compared to 3 of 3 (100.0%) hospitalized cases with a previous history of seizures. Previous history of seizures was not associated with seizure as a neurologic complication of influenza infection among hospitalized cases (p=0.21).	Level III n/a
Larcombe PJ, Moloney SE, Schmidt PA. Pandemic (H1N1) 2009: a clinical spectrum in the general paediatric population. Arch Dis Child. 2011;96(1):96-8.(77)	Design: Clinical case series (single centre) Period: May–August 2009 Location: Australia	Case definition: Patient (<18 years of age) hospitalized with laboratory-confirmed influenza virus infection Presentation: Febrile or respiratory illness Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=43 hospitalized cases Age group: Children Median age at hospitalization: 6 years (0.25–17 years)	**Hospitalization** n=2 of 43 (4.6%) hospitalized cases had pre-existing neuromuscular condition, including cerebral palsy (n=1) and Rett syndrome (n=1) (n=18 [41.9%] hospitalized cases had a pre-existing condition).	Level III n/a
Launes C, García-García JJ, Martínez-Planas A, et al. Clinical features of influenza disease in admitted children during the first postpandemic season and risk factors for hospitalization: a	Design: Case-control (multi-centre) Period: December 2010–March 2011	Case definition: Patient (6 months–18 years) hospitalized with influenza syndrome and laboratory-confirmed influenza virus infection Control definition: Medically-attended, non-	Seasonal influenza (2010–2011)	n=135 hospitalized cases and 137 non-hospitalized controls Age group: Children Median age of cases: 2.0 years (IQR: 1.0–6.0 years)	**Hospitalization** n=23 of 135 (17.0%) cases had neurological disease (n=52 [38.5%] hospitalized cases had one or more pre-existing conditions). Neurological disease was significantly associated with	Level II-2 Good

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
multicentre Spanish experience. Clin Microbiol Infect. 2013;19(3):E157-62.(78)	Location: Spain	hospitalized patient with laboratory-confirmed influenza virus infection Cases and controls matched by age, date of hospitalization, and province of residence Viral testing: rtRT-PCR		Median age of controls: 2.6 years (IQR: 1.2–6.3 years)	hospitalization (aOR: 17.18, 95% CI: 3.44–85.90, p=0.001).	
Launes C, García-García JJ, Martínez-Planas A, et al. 2009 H1N1: risk factors for hospitalization in a matched case-control study. Eur J Pediatr. 2012;171(7):1127-31.(79)	Design: Case-control (multi-centre) Period: July 2009–February 2010 Location: Spain	Case definition: Patient (6 months–18 years of age) hospitalized with influenza syndrome and community-acquired, laboratory-confirmed influenza virus infection Control definition: Medically-attended, non-hospitalized patient (6 months–18 years of age) with laboratory-confirmed influenza virus infection Cases and controls matched by date of hospitalization and province of residence Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=195 hospitalized cases and 184 non-hospitalized controls Age group: Children Median age of cases: 5.6 years (IQR: 1.4–10.5 years) Median age of controls: 6.2 years (IQR: 3.3–12.0 years)	**Hospitalization** n=31 of 195 (15.9%) hospitalized cases had neurologic disease (n=93 [47.7%] hospitalized cases had at least one pre-existing condition). Neurological disease was significantly associated with hospitalization (aOR: 3.0, 95% CI: 1.1–8.2, p=0.03).	Level II-2 Good
Lavallée PC, Labreuche J, Fox KM, Lavados P, Mattle H, Steg PG, et al. Influenza vaccination and cardiovascular risk in patients with recent TIA and stroke.	Design: Case-cohort (pooled) Period: June 2005–December 2008	AMISTAD Study cohort definition: Patient (≥18 years of age) with a non-disabling cerebral infarction documented by imaging or a TIA in the previous 10 days (n=618)	Seasonal influenza vaccine	n=23,110 of 23,353 (99.0%) patients with recent ischemic stroke or TIA enrolled in the AMISTAD Study, OPTIC Registry, and PERFORM Trial with available information on influenza vaccination at baseline and	**Post-vaccination (recurrence)** Influenza vaccination was not associated with the risk of recurrent stroke or TIA (propensity score-matched HR: 1.01, 95% CI: 0.88–1.17, p=0.89), stroke alone	Level II-2 Fair

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Neurology. 2014;82(21):1905-13.(80)	(AMISTAD Study), January 2007–December 2008 (OPTIC Registry), and February 2006–April 2008 (PERFORM Trial) for patient recruitment Location: France (AMISTAD Study) and multinational (OPTIC Registry [245 sites in 17 countries] and PERFORM Trial [802 sites in 46 countries])	OPTIC Registry cohort definition: Patient (≥45 years of age) with a recent non-cardioembolic TIA or minor stroke within the previous 6 months (n=3635) PERFORM Trial cohort definition: Patient (≥55 years of age) with a recent non-cardioembolic cerebral ischemic event, such as ischemic stroke, within the previous 3 months, or a TIA within the previous 8 days (n=19120) Influenza vaccination status: Self-reported questionnaire at enrollment (all three studies) and at each follow-up visit (PERFORM Trial only)		at least one post-baseline follow-up assessment n=5054 of 5747 (87.9%) vaccinated patients propensity score-matched to 5054 unvaccinated patients Age group: Adults Mean age (SD): of propensity score-matched vaccinated patients: 70.0 (7.5) years Mean age (SD) of propensity score-matched unvaccinated patients: 69.9 (7.9) years	(matched HR: 1.01, 95% CI: 0.86–1.18), or TIA alone (matched HR: 1.33, 95% CI: 0.30–5.96). Change in influenza vaccination status over time (time-varying analysis) was not associated with stroke (propensity score-aHR: 1.08, 95%: 0.95–1.22).	
Lee E, Seo JH, Kim HY, et al. Clinical characteristics and outcomes among pediatric patients hospitalized with pandemic influenza A/H1N1 2009 infection. Korean J Pediatr. 2011;54(8):329-34.(81)	Design: Clinical case series (single centre) Period: September 2009–February 2010 Location: South Korea	Case definition: Patient (<18 years of age) hospitalized with laboratory-confirmed, influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=72 hospitalized cases Age group: Children Median age at hospitalization: 6.0 years (range: 0.2–18 years)	**Hospitalization** n=3 of 72 (4.2%) hospitalized cases had neurologic disease (n=29 [40.3%] hospitalized cases had at least one underlying medical condition). **Hospitalization with pneumonia** n=1 of 54 (1.9%) hospitalized cases with pneumonia had	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					neurologic disease (n=16 [29.6%] hospitalized cases with pneumonia had at least one underlying medical condition). Neurologic disease was not associated with pneumonia among hospitalized cases (p=0.573).	
Lee MC, Kim HY, Kong SG, et al. Clinical Characteristics of Pandemic Influenza A (H1N1) 2009 Pediatric Infection in Busan and Gyeongsangnam-do: One Institution. Tuberc Respir Dis (Seoul). 2012;72(6):493-500.(82)	Design: Clinical case series (single centre) Period: August 2009–February 2010 Location: South Korea	Case definition: Patient (≤18 years of age) diagnosed with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=3777 medically-attended cases (n=221 [5.9%] hospitalized cases, including n=10 [0.3%] ICU cases) Age group: Children Mean age at hospitalization (SD): 6.7 (4.5) years Mean age at ICU admission (SD): 7.1 (4.3) years	**Hospitalization** n=19 of 221 (8.6%) hospitalized cases had neurologic disease (n=84 [38.0%] hospitalized cases had underlying diseases). Neurologic disease was a significant risk factor for hospitalization in medically-attended cases (OR: 15.74, 95% CI: 7.96–31.11). **ICU admission** n=4 of 10 (40.0%) ICU cases admitted to ICU had neurologic disease, including epilepsy, paralysis, hydrocephalus, and developmental disorder (n=9 [90.0%] ICU cases had underlying diseases).	Level III n/a
Lees EA, Carrol ED, Gerrard C, et al. Characterisation of acute respiratory infections at a United Kingdom paediatric teaching hospital: observational study	Design: Clinical case series (single centre) Period: April 2010–March 2011	Case definition: Patient (≤16 years of age) hospitalized with ARI and community-acquired, laboratory-confirmed respiratory virus infection, including influenza	Pandemic influenza A(H1N1)pdm09	n=82 hospitalized cases Age group: Children Median age at hospitalization: 1.3 years (range: 0.1–15 years)	**Hospitalization** n=11 of 82 (13.4%) hospitalized cases had a neurological comorbidity (n=35 [42.7%] hospitalized cases had a comorbidity).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
assessing the impact of influenza A (2009 pdmH1N1) on predominant viral pathogens. BMC Infect Dis. 2014;14:343.(83)	Location: UK	Viral testing: Multiplex RT-PCR, with RT-PCR subtype confirmation				
Lehners N, Geis S, Eisenbach C, Neben K, Schnitzler P. Changes in severity of influenza A(H1N1)pdm09 infection from pandemic to first postpandemic season, Germany. Emerg Infect Dis. 2013;19(5):748-55.(84)	Design: Clinical case series (single centre) Period: May 2009–April 2011 Location: Germany	Case definition: Patient hospitalized with ILI and laboratory-confirmed influenza virus infection (a severe case was defined as those admitted to ICU or died while hospitalized) Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09 Seasonal (post-pandemic) influenza A(H1N1)pdm09 (2010–2011)	n=178 hospitalized pandemic and seasonal cases (n=50 [28.1%] severe cases, including n=15 [8.4%] fatal cases) n=102 hospitalized pandemic cases and 76 hospitalized seasonal (post-pandemic) cases Age group: Mixture of children and adults (hospitalization; ICU admission or death); adults (death) Mean age at hospitalization: 18.2 years for pandemic cases and 38 years for seasonal cases (n=85 of 178 [47.8%] hospitalized cases <15 years of age) Median age at death: 57 years (range: 18–85 years)	**Hospitalization (pandemic)** n=15 of 102 (14.7%) hospitalized pandemic cases had neurologic impairment (n=52 [51.0%] hospitalized pandemic cases had an underlying medical condition). **Hospitalization (seasonal)** n=8 of 76 (10.5%) hospitalized seasonal (post-pandemic) cases had neurologic impairment (n=57 [75.0%] hospitalized seasonal [post-pandemic] cases had an underlying medical condition). **ICU admission or death (pandemic and seasonal A[H1N1]pdm09)** n=7 of 50 (14.0%) ICU or fatal cases had neurologic impairment (n=45 [90.0%] ICU or fatal cases had an underlying medical condition). Neurologic impairment was not associated with severe disease (ICU admission or death) among hospitalized cases (p=0.79).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Death (pandemic and seasonal A[H1N1]pdm09; ≥18 years of age) n=1 of 15 (6.7%) fatal cases had neurologic impairment (Parkinson disease and epilepsy) (n=14 [93.3%] fatal cases had an underlying medical condition). **Pandemic vs. seasonal (hospitalization)** The proportion with neurologic impairment was not significantly different between hospitalized pandemic and seasonal influenza A(H1N1)pdm09 cases (14.7% vs. 10.5%, p=0.41).	
Libster R, Bugna J, Coviello S, Hijano DR, Dunaiewsky M, Reynoso N, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med. 2010;362(1):45-55.(85)	Design: Population case series Period: May–July 2009 Location: Argentina	Case definition: Patient (<18 years of age) hospitalized with laboratory-confirmed influenza virus infection Presentation: ARI (undefined) or fever (≥38.3°C) Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=251 hospitalized cases (n=13 [5.2%] fatal cases) Age group: Children Median age at hospitalization: 0.8 years (range: <0.1–18.8 years) Median age at death: 1.6 years (range: <0.1–14.5 years)	**Hospitalization** n=21 of 245 (8.6%) hospitalized cases had neurologic disease (n=81 of 241 [33.6%] hospitalized cases had any pre-existing condition). **Death** n=4 of 13 (30.8%) fatal cases had pre-existing neurologic disorder (n=9 [69.2%] fatal cases had any pre-existing condition). Neurologic disease was a significant risk factor for death among hospitalized cases (OR: 5.62, 95% CI: 1.13–22.63, p=0.003).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Liu L, Zhang RF, Lu HZ, et al. Sixty-two severe and critical patients with 2009 influenza A (H1N1) in Shanghai, China. Chin Med J (Engl). 2011;124(11):1662-6.(86)	Design: Clinical case series (single centre) Period: November 2009–January 2010 Location: China	Case definition: Patient hospitalized with laboratory-confirmed influenza virus infection Viral testing: Subtype-specific RT-PCR	Pandemic influenza A(H1N1)pdm09	n=62 hospitalized cases Age group: Adults Median age at hospitalization: 40 years (range: 18–75 years)	**Hospitalization** n=3 of 62 (4.8%) hospitalized cases had neurological disease, 1 (1.6%) had cerebrovascular disease, and 1 (1.6%) had seizures (n=34 [54.8] hospitalized cases had any comorbidity).	Level III n/a
Lockman JL, Fischer WA, Perl TM, Valsamakis A, Nichols DG. The critically ill child with novel H1N1 influenza A: a case series. Pediatr Crit Care Med. 2010;11(2):173-8.(87)	Design: Clinical case series (single centre) Period: June–August 2009 Location: USA	Case definition: Patient (<22 years of age) admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: DFA test or viral culture, with rtRT-PCR subtype confirmation	Pandemic influenza A(H1N1)pdm09	n=13 ICU cases. Age group: Children Median age at ICU admission: 9.5 years (range: 0.4–21.9 years)	**ICU admission** n=5 of 13 (38.5%) ICU cases had neurologic/neuromuscular disease (n=12 [92.3%] ICU cases had underlying comorbid illness).	Level III n/a
Louie JK, Gavali S, Acosta M, et al. Children hospitalized with 2009 novel influenza A(H1N1) in California. Arch Pediatr Adolesc Med. 2010;164(11):1023-31.(88)	Design: Population case series Period: April–August 2009 Location: USA (California)	Case definition: Patient (<18 years of age) hospitalized for ≥24 hours with influenza-like symptoms and laboratory-confirmed influenza virus infection (a fatal case was defined as those who died and had influenza-like symptoms with laboratory-confirmed influenza virus infection and influenza listed in the death certificate as cause of death) Presentation: Fever and	Pandemic influenza A(H1N1)pdm09	n=345 hospitalized cases (n=96 [27.8%] ICU and/or fatal cases, including 9 [2.6%] fatal cases) Age group: Children Median age at hospitalization: 6 years (range: <0.1–17 years) Median age at ICU admission and/or death: 7 years (range: <0.1–17 years) Median age at death: 5 years (range: 0.5–14 years)	**Hospitalization** n=59 of 345 (17.1%) cases had chronic neurologic disease, including cerebral palsy/developmental delay (n=41), seizure disorder (n=31), and other neurologic disease (n=13) (n=212 [61.4%] hospitalized cases had ACIP-defined influenza risk factors). **ICU admission or death** n=28 of 96 (29.2%) ICU and/or fatal cases had chronic neurologic disease, including cerebral palsy/developmental delay	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		cough, sore throat, or clinical suspicion for influenza infection Viral testing: RT-PCR Risk group definition: ACIP			(n=21), seizure disorder (n=14), and other neurologic disease (n=7) (n=70 [72.9%] ICU and/or fatal cases had ACIP-defined influenza risk factors). In univariate analysis, chronic neurologic disease was significantly associated with ICU admission and/or death (OR: 2.8, 95% CI: 1.6–5.0, p<0.05), as well as cerebral palsy/developmental delay (OR: 3.1, 95%CI: 1.6–6.0, p<0.05), seizure disorder (OR: 2.2, 95% CI: 1.1–4.8, p<0.05), but not other neurologic disease (OR: 3.1, 95% CI: 1.0–9.4). In multivariate analysis, cerebral palsy/developmental delay remained significantly associated with ICU admission and/or death (aOR: 3.5, 95% CI: 1.7–7.4, p<0.05). **Death** n=5 of 9 (55.6%) fatal cases had chronic neurologic disease, including cerebral palsy/developmental delay (n=4) (n=8 [88.9%] fatal cases had ACIP-defined influenza risk factors).	
Louie JK, Schechter R, Honarmand S, et al. Severe pediatric influenza in California, 2003-2005:	Design: Population case series Period:	Case definition: Patient (<18 years of age) admitted to ICU or died while hospitalized with laboratory-confirmed	Seasonal influenza A and B (2003–2004 and 2004–2005)	n=160 ICU or fatal cases (n=15 [9.4%] fatal cases) Age group: Children	**ICU admission or death** n=36 of 160 (22.5%) ICU or fatal cases had an underlying neurological/neuromuscular disorder, including seizure	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
implications for immunization recommendations. Pediatrics. 2006;117(4):e610-8.(89)	December 2003–May 2005 Location: USA (California)	influenza virus infection Presentation: Clinical syndrome consistent with influenza or complications of influenza, including lower respiratory tract infection, ARDS, apnea, cardiopulmonary arrest, myocarditis, Reye or Reye-like syndrome, or acute CNS system syndrome Viral testing: RT-PCR Risk group definition: ACIP and AAP		Median age at ICU admission or death: 1.5 years (range: <0.1–17.9 years)	disorder (n=19), cerebral palsy (n=8), developmental delay (n=14), hypoxic/anoxic encephalopathy (n=3), microcephaly (n=4), and other neurological/neuromuscular disorders (n=12) (n=85 [53.1%] ICU or fatal cases had one or more underlying medical conditions). **Death** n=5 of 15 (33.3%) fatal cases had an underlying neurological/neuromuscular disorder, including seizure disorder (n=3), cerebral palsy (n=1), developmental delay (n=1), microcephaly (n=1), and other neurological/neuromuscular disorders (n=2) (n=12 [80.0%] fatal cases had an underlying medical condition).	
Ma HY, Wu JL, Lu CY, et al. Risk factors associated with severe influenza virus infections in hospitalized children during the 2013 to 2014 season. J Microbiol Immunol Infect. 2016;49(3):387-93.(90)	Design: Clinical case series (single centre) Period: October 2013–May 2014 Location: Taiwan	Case definition: Patient (children; age range not defined) hospitalized with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR, RIDT, or viral culture	Seasonal influenza A and B (2013–2014)	n=110 hospitalized cases (n=19 [17.3%] ICU cases) Age group: Children Median age at hospitalization: 2.6 years (IQR: 1.0–6.3 years) Median age at ICU admission: 2.3 years (IQR: 1.4–10.4 years)	**Hospitalization** n=20 of 110 (18.2%) hospitalized cases had neuromuscular disease (n=53 [48.2%] hospitalized cases had underlying medical conditions). **ICU admission** n=8 of 19 (42.1%) ICU cases had neuromuscular disease (n=13 [68.4%] ICU cases had underlying medical conditions).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Neuromuscular disease was significantly associated with ICU admission among hospitalized cases in univariate analysis (p=0.007), but not in multivariate analysis (aOR: 4.41, 95% CI: 0.62–13.36, p=0.14).	
Macesic N, Kotsimbos TC, Kelly P, Cheng AC. Hospital-acquired influenza in an Australian sentinel surveillance system. Med J Aust. 2013;198(7):370-2.[91]	Design: Population case series Period: April–November 2010 and April–November 2011 Location: Australia	Case definition: Patient (adults; age range not defined) hospitalized with laboratory-confirmed influenza virus infection Viral testing: RT-PCR (no subtyping performed)	Seasonal influenza A and B (2010 and 2011) n=539 of 598 (90.1%) hospitalized cases infected with influenza A and 60 (10.0%) with influenza B	n=598 hospitalized cases Age group: Adults	**Hospitalization** n=52 of 598 (8.7 %) hospitalized cases had chronic neurological disease (n=436 [72.9%] hospitalized cases had any chronic comorbidity).	Level III n/a
Martin-Loeches I, Díaz E, Vidaur L, et al. Pandemic and post-pandemic influenza A (H1N1) infection in critically ill patients. Crit Care. 2011;15(6):R286.[92] *(Supplemented with additional details from Martín-Loeches I, et al. Chest. 2011;139(3):555-62.[157])*	Design: Population case series Period: May–December 2009 (pandemic) and December 2010–February 2011 (post-pandemic) Location: Spain	Case definition: Patient (≥15 years of age) admitted to ICU for acute respiratory failure with laboratory-confirmed influenza virus infection Presentation: Fever (>38°C) and respiratory symptoms consistent with cough, sore throat, myalgia, or ILI Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A(H1N1)pdm09 (2010–2011)	n=648 pandemic ICU cases (n=141 [21.8%] fatal pandemic ICU cases) and 349 seasonal (post-pandemic) ICU cases (n=105 [30.1%] fatal seasonal ICU cases) Age group: Predominantly adults Median age at ICU admission: 34 years (IQR: 44–54 years) for pandemic cases and 40 years (IQR: 51–59 years) for seasonal cases	**ICU admission (pandemic)** n=24 of 648 (3.7%) pandemic ICU cases had neuromuscular disease (n=465 [71.8%] pandemic ICU cases had at least one underlying medical condition). **ICU admission (seasonal)** n=4 of 349 (1.1%) seasonal (post-pandemic) ICU cases had neuromuscular disease (n=258 [73.9%] seasonal [post-pandemic] ICU cases had at least one underlying medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Pandemic vs. seasonal (ICU admission) The proportion with neuromuscular disease was significantly different between pandemic and seasonal influenza A(H1N1)pdm09 ICU cases (3.7% vs. 1.1%, p=0.02). **Death (pandemic)** n=6 of 141 (4.3%) fatal pandemic ICU cases had neuromuscular disease (n=112 [79.4%] fatal pandemic ICU cases had at least one underlying medical condition). Neuromuscular disease was not associated with death among pandemic ICU cases (p=0.69). **Death (seasonal)** n=2 of 105 (1.9%) fatal seasonal (post-pandemic) cases had neuromuscular disease (n=81 [77.1%] fatal seasonal [post-pandemic] cases had at least one underlying medical condition). Neuromuscular disease was not associated with death among seasonal (post-pandemic) ICU cases (p=0.38).	
Meury S, Zeller S, Heininger U.	Design: Clinical case	Case definition: Patient (children; age range not	Seasonal influenza A and	n=56 hospitalized cases	**Hospitalization** n=2 of 56 (3.6%) hospitalized	Level III

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Comparison of clinical characteristics of influenza and respiratory syncytial virus infection in hospitalised children and adolescents. Eur J Pediatr. 2004;163(7):359-63.(93)	series (single centre) Period: 2001–2003 Location: Switzerland	defined) hospitalized with respiratory symptoms and laboratory-confirmed respiratory virus infection, including influenza Viral testing: Multiplex RT-PCR	B (2001–2002 and 2002–2003) n=42 of 56 (75.0%) hospitalized cases infected with influenza A and 14 (25.0%) with influenza B	Age group: Children Median age at hospitalization: 2.3 years (IQR: 1–3.1 years) for influenza A infected cases and 6.2 years (IQR: 4.7–9.5 years) for influenza B infected cases	cases had underlying CNS abnormalities (n=15 [26.8%] hospitalized cases had any underlying condition).	n/a
Michielsens B, Wilms G, Marchal G, Carton H. Serial magnetic resonance imaging studies with paramagnetic contrast medium: assessment of disease activity in patients with multiple sclerosis before and after influenza vaccination. Eur Neurol. 1990;30(5):258-9.(94)	Design: Uncontrolled trial Period: NR Location: Belgium	Trial cohort definition: Patient with MS presenting with a relapsing-remitting course but in a stable phase at the onset of the study and without immunosuppressive treatment Intervention: Influenza vaccine (inactivated trivalent vaccine containing A/Leningrad 360/86 [H3N2], A/Singapore 6/86 [H1N1] and B/Ann Arbor 1/86)	Seasonal influenza vaccine	n=11 MS patients received influenza vaccine Age group: NR	**Post-vaccination (exacerbation)** No clinical exacerbation of MS occurred during the pre- (3 weeks before) or post-vaccination (3 weeks after) observation period. The total number of contrast-enhanced lesions and new enhanced spots was not higher in the post-vaccination period than in the pre-vaccination period; the difference between the two periods is not statistically significant (RR: 0.45, 95% CI: 0.035–5.843).	Level III n/a
Miller AE, Morgante LA, Buchwald LY, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. Neurology. 1997;48(2):312-4.(95)	Design: Double-blind, non-randomized, placebo-controlled trial (multi-centre) Period: 1993 Location: USA	Trial cohort definition: Patient with a diagnosis of clinically definite, relapsing-remitting MS and ambulatory with no more than a unilateral aid, excluding those who experienced an acute exacerbation or treatment with corticosteroids in the previous four weeks, had	Seasonal influenza vaccine	n=49 MS patients received influenza vaccine and 54 received placebo Age group: NR	**Post-vaccination (exacerbation)** During 28 days after vaccination, no significant difference was observed in frequency of MS exacerbations in the influenza vaccine recipient group (n=3) and placebo recipient group (n=2). During six months after	Level II-1 n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		not been treated with immunosuppressive medications within the preceding six months, or had a history of prior adverse reaction to influenza vaccine or egg products Intervention: Influenza vaccine (standard influenza vaccine) and placebo (vaccine diluent without virus)			vaccination, no significant difference was observed in attack rate of MS exacerbations in the influenza vaccine recipient group (n=11 attacks; annual attack rate: 0.45) and placebo recipient group (n=6 attacks; annual attack rate: 0.22). The mean time of onset of MS relapse after vaccination was longer for influenza vaccine recipients (mean [SD]: 91.5 [61.9] days) compared to placebo recipients (mean [SD]: 55.3 [36.4] days), but the difference between means was not significant. There was no significant difference in the numbers of MS patients who worsened in the six-month study period (n=8 vaccine recipient group and n=10 placebo recipient group). There was no significant difference in the mean change in the Kurtzke Extended Disability Status Scores of MS patients (vaccine: 0.02; placebo: 0.09). Influenza vaccination in MS patients is neither associated with an increased	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					exacerbation rate nor a change in disease course in the six months period following vaccination.	
Milne BG, Williams S, May ML, Kesson AM, Gillis J, Burgess MA. Influenza A associated morbidity and mortality in a Paediatric Intensive Care Unit. Commun Dis Intell Q Rep. 2004;28(4):504-9.(96)	Design: Clinical case series (single centre) Period: 2003 Location: Australia	Case definition: Patient (children; age range not defined) admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: DFA test (confirmed by viral culture) or viral culture	Seasonal influenza A (2003) n=22 of 22 (100.0%) ICU cases infected with influenza A(H3N2)	n=22 ICU cases Age group: Children Median age at ICU admission: 4.1 years (range: 0.3–13 years)	**ICU admission** n=5 of 22 (22.7%) ICU cases had pre-existing neurologic morbidities, including developmental delay (n=3), seizures (n=2), and cerebral palsy (n=1) (n=11 [50.0%] ICU cases had pre-existing morbidities).	Level III n/a
Miroballi Y, Baird JS, Zackai S, et al. Novel influenza A(H1N1) in a pediatric health care facility in New York City during the first wave of the 2009 pandemic. Arch Pediatr Adolesc Med. 2010;164(1):24-30.(97)	Design: Clinical case series (multi-centre) Period: May–July 2009 Location: USA	Case definition: Patient (≤18 years of age) hospitalized with ILI and laboratory-confirmed influenza virus infection Presentation: ILI: chief complaint reported to be: fever and cough, fever and sore throat, and/or flu or influenza Viral testing: Enzyme immunoassay, DFA test, viral culture, and/or RT-PCR (n=54 of 115 [47.0%] cases additionally confirmed by RT-PCR to be pandemic influenza A(H1N1)pdm09)	Pandemic influenza A(H1N1)pdm09	n=115 hospitalized cases Age group: Children Median age at hospitalization: 4.8 years (range: <0.1–18 years)	**Hospitalization** n=12 of 115 (10.4%) hospitalized cases had an underlying neuromuscular condition (n=93 [80.9%] hospitalized cases had at least one underlying condition).	Level III n/a
Mistry RD, Fischer JB, Prasad PA, Coffin SE, Alpern ER. Severe complications in influenza-like illnesses.	Design: Clinical case series (single centre)	Case definition: Patient (≤19 years of age) presented to the ED with moderate to severe ILI and laboratory-confirmed	Seasonal influenza A and B and pandemic influenza A(H1N1)pdm09	n=60 ED cases with influenza infection Age group: Predominantly children	**ED admission** n=9 of 60 (15.0%) ED cases had a neurologic condition (n=39 [65.0%] ED cases had any high-risk condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Pediatrics. 2014;134(3):e684-90.(98)	Period: 2008–2010 Location: USA	respiratory virus infection, including influenza Presentation: ILI: fever plus cough or sore throat, in the absence of an alternative cause Viral testing: Multiplex RT-PCR Risk group definition: ACIP		Median age at ED presentation: 3.8 years		
Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. Mult Scler. 1997;3(4):243-7.(99)	Design: Double-blind, non-randomized, placebo-controlled trial Period: NR Location: USA	Trial cohort definition: Patient with a diagnosis of clinically definite, relapsing-remitting MS and ambulatory with no more than a unilateral aid (intervention group receiving influenza vaccine or placebo) and age- and sex-matched normal subjects (control group receiving influenza vaccine) Intervention: Influenza vaccine (inactivated whole-virus 1993–1994 season formulation) and placebo (vaccine diluent without virus)	Seasonal influenza vaccine (1993–1994)	n=11 MS patients received influenza vaccine, 8 MS patients received placebo, and 9 controls (age- and sex-matched normal subjects) received influenza vaccine Age group: Adults Mean age of MS patients (SD): 40.2 (10.3) years (range: 28–60 years)	**Post-vaccination (exacerbation)** Frequency of MS exacerbation was similar in influenza vaccine recipient group (n=3 of 11) and placebo group (n=2 of 8). There was no significant difference in the mean change in the Kurtzke Extended Disability Status Scores of MS patients in influenza vaccine recipient and placebo recipient groups. Influenza vaccination did not cause or protect against exacerbation of MS.	Level II-1 n/a
Monmany J, Rabella N, Margall N, Domingo P, Gich I, Vázquez G. Unmasking influenza virus infection in patients attended to in	Design: Clinical case series (single centre) Period:	Case definition: Patient (≥18 years of age) presented to the ED with influenza syndrome, deterioration of a previous condition, or	Seasonal influenza A (1999–2000)	n=99 ED cases with influenza A infection Age group: Adults	**ED presentation (exacerbation)** n=13 ED cases with influenza A infection experienced exacerbation of dementia (total ED cases	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
the emergency department. Infection. 2004;32(2):89-97.[100]	December 1999–February 2000 Location: Spain	abrupt onset of symptoms like dyspnea, delirium, falls, syncope, vomiting and incontinence Presentation: Influenza syndrome with at least five of the following: abrupt onset, fever, chills, malaise, cough, coryza, muscle aches and disproportionate prostration, aching and fever with respect to catarrhal symptoms Viral testing: Indirect immunofluorescence assay (n=99 of 136 [72.8%] recruited patients positive for influenza A antigen)			with influenza A infection and dementia NR). Dementia was the second most exacerbated pre-existing disease after chronic respiratory disease among ED cases with influenza A infection (n=35).	
Moore DL, Vaudry W, Scheifele DW, et al. Surveillance for influenza admissions among children hospitalized in Canadian immunization monitoring program active centers, 2003-2004. Pediatrics. 2006;118(3):e610-9.[101]	Design: Clinical case series (multi-centre) Period: 2003–2004 Location: Canada	Case definition: Patient (children; age range not defined) hospitalized for influenza or related complications with community-acquired, laboratory-confirmed influenza virus infection, excluding those hospitalized for unrelated reasons but with concomitant influenza Viral testing: Viral culture (n=205 of 505 [40.6%]), DFA (n=184 [36.4%]), or not specified	Seasonal influenza A and B (2003–2004) n=500 of 505 (99.0%) hospitalized cases infected with influenza A and 5 (0.1%) with influenza B	n=505 hospitalized cases Age group: Children Median age at hospitalization: 1.7 years (range: <0.1–18 years)	**Hospitalization** n=59 of 505 (11.7%) hospitalized cases had neurologic diseases, including developmental delay with seizures, hydrocephalus, microcephaly, or neuromuscular abnormality (n=18); seizure disorders (n=12); cerebral palsy (n=10); chronic encephalopathy (n=6); neuromuscular disorders (n=6); hydrocephalus (n=3); developmental delay without other abnormality (n=3); and pseudotumor cerebri (n=1)	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					(n=212 [42.0%] hospitalized cases had a chronic underlying condition).	
Morgan CI, Hobson MJ, Seger B, Rice MA, Staat MA, Wheeler DS. 2009 pandemic influenza A (H1N1) in critically ill children in Cincinnati, Ohio. Pediatr Crit Care Med. 2012;13(3):e140-4.[102]	Design: Clinical case series (single centre) Period: December 2006–May 2007, November 2007–May 2008, December 2008–April 2009 (seasonal), and June–November 2009 (pandemic) Location: USA	Case definition: Patient (children; age range not defined) hospitalized with laboratory-confirmed influenza virus infection Viral testing: RIDT, RT-PCR, or viral culture Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2006–2007 through 2008–2009)	n=553 hospitalized pandemic and seasonal cases (n=45 [8.1%] pandemic ICU cases and 54 [9.8%] seasonal ICU cases) Age group: Children Median age at ICU admission: 8.9 years (IQR: 4.7–12.8 years) for pandemic cases and 5.7 years (IQR: 1.3–10.7 years) for seasonal cases	**ICU admission (pandemic)** n=12 of 45 (26.7%) pandemic ICU cases had neurologic conditions (n=29 [64.4%] pandemic ICU cases had comorbid conditions). **ICU admission (seasonal)** n=13 of 54 (24.1%) seasonal ICU cases had neurologic conditions (n=22 [40.7%] seasonal ICU cases had comorbid conditions). **Pandemic vs. seasonal (ICU admission)** The proportion with neurologic conditions was not significantly different between pandemic influenza A(H1N1)pdm09 and seasonal influenza A and B ICU cases (26.7% vs. 24.1%, p=0.82).	Level III n/a
Morris SK, Parkin P, Science M, et al. A retrospective cross-sectional study of risk factors and clinical spectrum of children admitted to hospital with pandemic H1N1 influenza as compared to influenza A. BMJ Open. 2012;2(2):e000310.[103]	Design: Clinical case series (single centre) Period: 2004–2009 (seasonal) and May–July 2009 and September–December 2009	Case definition: Patient (<18 years of age) hospitalized with community-acquired, laboratory-confirmed influenza virus infection Viral testing: DFA followed by RT-PCR for pandemic influenza or DFA and/or viral culture for seasonal influenza	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A (2004–2005 through 2008–2009)	n=176 hospitalized pandemic cases (n=32 [18.2%] pandemic ICU cases) and 200 hospitalized seasonal cases (n=31 [15.5%] seasonal ICU cases) Age group: Children Median age at hospitalization: 6.5 years (IQR: 3.0–10.6 years) for pandemic cases and 3.3	**Hospitalization (pandemic)** n=21 of 176 (11.9%) hospitalized pandemic cases had neurological impairment. **Hospitalization (seasonal)** n=26 of 200 (13.0%) hospitalized seasonal cases had neurological impairment. **ICU admission (pandemic)** n=6 of 32 (18.8%) pandemic ICU cases had neurological	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
	(pandemic) Location: Canada			years (IQR: 1.4–7.8 years) for seasonal cases	impairment. **ICU admission (seasonal)** n=8 of 31 (25.8%) seasonal ICU cases had neurological impairment. **Pandemic vs. seasonal (hospitalization; ICU admission)** The proportion with neurologic impairment was not significantly different between hospitalized pandemic influenza A(H1N1)pdm09 and seasonal influenza A cases (11.9% vs. 13.0%, p=0.76) and pandemic and seasonal cases admitted to ICU (18.8% vs. 25.8%, p=0.56).	
Muhammad Ismail HI, Teh CM, Lee YL; National Paediatric H1N1 Study Group. Neurologic manifestations and complications of pandemic influenza A H1N1 in Malaysian children: what have we learnt from the ordeal? Brain Dev. 2015;37(1):120-9.[(104)]	Design: Population case series Period: June–November 2009 Location: Malaysia	Case definition: Patient (≤12 years of age) hospitalized for ILI with neurologically complicated illness and laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=103 hospitalized cases with neurologically complicated illness Age group: Children Mean age at hospitalization (SD): 4.2 (3.3) years	**Hospitalization with neurologically complicated illness** 28% of 103 hospitalized cases with neurologically complicated illness had pre-existing neurologic illnesses, including epilepsy or seizure disorders (n=17), cerebral palsy (n=2), neuro-genetic disorders (n=3), and neuromuscular disorders (n=2) (n=33 [32.0%] hospitalized cases with neurologically complicated illness had premorbid conditions).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Post-infection (exacerbation) n=16 (94.1%) of 17 cases with underlying epilepsy or seizure disorders experienced breakthrough or exacerbation of seizures.	
Myers LW, Ellison GW, Lucia M, et al. Swine influenza virus vaccination in patients with multiple sclerosis. J Infect Dis. 1977;136 Suppl:S546-54.(105)	Design: Double-blind, randomized, placebo-controlled trial Period: NR Location: USA	Trial cohort definition: Patient (≥24 years of age) with MS without a history of allergic reaction to eggs or influenza virus vaccines and not receiving corticosteroids or other immunomodulating drugs Intervention groups: Influenza vaccine (inactivated, whole A/New Jersey/76 and A/Victoria/75), placebo (vaccine diluent without virus), and untreated	Seasonal influenza vaccine	n=33 MS patients received influenza vaccine, 33 received placebo, and 22 untreated Age group: Adults Mean age of patients receiving influenza vaccine: 43 years (range: 26–64 years) Mean age of patients receiving placebo: 43 years (range: 25–64 years) Mean age of untreated patients: 44 years (range: 22–61 years)	**Post-vaccination (relapse)** During the three-month follow-up period, the frequency of MS relapses was the same in influenza vaccine recipient group (n=4 of 33; relapse rate: 0.5) and placebo group (n=4 of 33; relapse rate: 0.5), but slightly higher in the untreated group (n=4 of 22; relapse rate: 0.7).	Level I Fair
Mytton OT, Rutter PD, Mak M, Stanton EA, Sachedina N, Donaldson LJ. Mortality due to pandemic (H1N1) 2009 influenza in England: a comparison of the first and second waves. Epidemiol Infect. 2012;140(9):1533-41.(106) *(Supplemented with*	Design: Population case series Period: June 2009–April 2010 (children: June 2009–March 2010) Location: UK (England)	Case definition: Death associated with influenza virus infection with/without record of pandemic influenza A(H1N1) on death certificate Viral testing: Specific methods NR (n=353 of 361 [97.8%] cases with laboratory-confirmed influenza infection; 100.0% of pediatric	Pandemic influenza A(H1N1)pdm09	n=361 fatal cases (n=357 [98.9%] fatal cases with available information on underlying health status; n=70 [19.4%] fatal cases <18 years of age) Age group: Predominantly adults (subgroup reporting death outcome for children <18 years of age) Median age at death: 44 years (IQR: 26–60 years;	**Death** n=73 of 357 (20.4%) fatal cases had chronic neurological disease, including other neurodevelopmental delay (n=34), epilepsy (n=21), cerebral palsy (n=17), cerebrovascular disease (n=17), neurocognitive disease (n=8), quadriplegia/paraplegia (n=5), neuromuscular disease (n=5), spinal	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
additional details from Sachedina N, Donaldson LJ. Lancet. 2010;376(9755):1846-52.(159) [Pediatric deaths])		cases with laboratory-confirmed influenza infection)		n=87 of 361 [24.1%] fatal cases <25 years of age)	muscular dystrophy (n=3), and other neurological disease (n=11), and 17 (4.8%) had stroke/TIA (n=252 [70.6%] fatal cases had any risk factor). Individuals with chronic neurological disease, including neurodevelopmental, neurodegenerative conditions and dementia, but excluding stroke and TIA, had a significantly higher age-SMR (450 deaths per million population, 95% CI: 320–600) than those with no risk factors (450 vs. 2.4 deaths per million, p<0.001). Individuals with pre-existing stroke or TIA had a significantly higher age-SMR rate (4.3 deaths per million, 95% CI: 2.4–7.2) than those with no risk factors (4.3 vs. 2.4 deaths per million, p<0.001). **Death (<18 years of age)** n=38 of 70 (54.3%) fatal cases had any chronic neurological disease, including cerebral palsy (n=22) and epilepsy (n=22) (n=55 [78.6%] fatal cases had any risk factor). The highest age-SMR for a pre-existing disorder in	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					individuals between 6 months and 18 years of age was for chronic neurological disease (1536 deaths per million, 95% CI: 988–2242).	
Norfolk SG, Hollingsworth CL, Wolfe CR, et al. Rescue therapy in adult and pediatric patients with pH1N1 influenza infection: a tertiary center intensive care unit experience from April to October 2009. Crit Care Med. 2010;38(11):2103-7.[107]	Design: Clinical case series (single centre) Period: April–October 2009 Location: USA	Case definition: Patient hospitalized with laboratory-confirmed influenza virus infection Viral testing: RT-PCR with subtype-specific primers for confirmed cases or testing methods without further identification of subtype for probable cases	Pandemic influenza A(H1N1)pdm09	n=127 hospitalized cases (n=33 [26.0%] ICU cases) Age group: Mixture of children and adults Age at ICU admission: n=12 of 33 (36.4%) ICU cases <18 years of age	**ICU admission** n=4 of 33 (12.1%) ICU cases had seizure disorder (n=31 [93.9%] ICU cases had significant comorbid medical conditions).	Level III n/a
Okumura A, Nakagawa S, Kawashima H, et al. Deaths associated with pandemic (H1N1) 2009 among children, Japan, 2009-2010. Emerg Infect Dis. 2011;17(11):1993-2000.[108]	Design: Population case series Period: May 2009–March 2010 Location: Japan	Case definition: Death associated with laboratory-confirmed influenza virus infection in patients <20 years of age Viral testing: rtRT-PCR (n=38 of 41 [92.7%]) or RIDT (positive test assumed to be pandemic influenza A[H1N1]pdm09)	Pandemic influenza A(H1N1)pdm09	n=41 fatal cases Age group: Children Median age at death: 4.9 years (range: 0.6–17.2 years)	**Death** n=11 of 41 (26.8%) fatal cases had neurologic disorders (n=9 [22.0%] with ≥2 neurologic disorders and 7 [17.1%] with comorbid respiratory disorders), including cerebral palsy, mental retardation, epilepsy, or neuromuscular disease, and 6 (14.6%) had a history of febrile seizures (n=14 [34.1%] fatal cases had at least one pre-existing condition).	Level III n/a
Ono S, Ono Y, Matsui H, Yasunaga H. Factors associated with hospitalization for seasonal influenza in a Japanese nonelderly cohort. BMC Public	Design: Population case series Period: October 2013–December	Case definition: Patient (<65 years of age) diagnosed with laboratory-confirmed influenza virus infection (ICD-10 code: J10)	Seasonal influenza A and B (2013–2014 and 2014–2015) n=188 of 276 (68.1%)	n=88,054 medically-attended cases (n=276 [0.3%] hospitalized cases) Age group: Mixture of children and adults	**Hospitalization** n=33 of 276 (12.0%) hospitalized cases had neurologic disease and 4 (1.4%) had cerebrovascular disease.	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Health. 2016;16(1):922.[109]	2014 Location: Japan	Viral testing: RIDT (>95% of patients) or other non-specified method Risk group definition: Comorbid conditions identified by WHO-ATC or ICD-10 codes, including ICD-10 codes G00–G99 for neurologic disease and I60–I69 for cerebrovascular disease	hospitalized cases infected with influenza A, 78 (28.3%) with influenza B, and 10 (3.6%) with influenza A and B	Age of hospitalized cases: n=191 of 276 [69.2%] hospitalized cases <18 years of age	Neurologic disease was significantly associated with hospitalization in medically-attended cases (aHR: 2.62, 95% CI: 1.68–4.11, p<0.001) analysis. Cerebrovascular disease was not significantly associated with hospitalization in medically-attended cases (aHR: 2.48, 95% CI: 0.88–6.97, p=0.084).	
Ostovar GA, Rubin LG, Rajan S, Sood SK, Kohn N. Comparison of the clinical features of children hospitalized with pandemic 2009 A:H1N1 and seasonal influenza. Clin Pediatr (Phila). 2011;50(4):348-54.[110]	Design: Clinical case series (single centre) Period: January 2004–March 2009 (seasonal) and April–August 2009 (pandemic) Location: USA	Case definition: Patient (children; age range not defined) hospitalized with laboratory-confirmed influenza virus infection Viral testing: RT-PCR for pandemic influenza and DFA testing or viral culture (n=38 of 80 [47.5%]) or RIDT (n=42 [52.5%]) for seasonal influenza Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2004–2005 through 2008–2009)	n=67 hospitalized pandemic cases and 80 hospitalized seasonal cases Age group: Children Median age at hospitalization: 6.5 years for pandemic cases and 1.3 years for seasonal cases (100.0% of hospitalized cases <18 years of age)	**Hospitalization (pandemic)** n=7 of 67 (10.4%) pandemic cases had an underlying neuromuscular disease (n=48 [71.6%] had an underlying condition). **Hospitalization (seasonal)** n=7 of 80 (8.8%) seasonal cases had an underlying neuromuscular disease (n=39 [48.8%] had an underlying condition). **Pandemic vs. seasonal (hospitalization)** The proportion with neuromuscular disease was not significantly different between hospitalized pandemic influenza A(H1N1)pmd09 and seasonal influenza A and B cases (10.4% vs. 8.8%, p>0.05).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Owayed AF, Husain EH, Al-Khabaz A, Al-Qattan HY, Al-Shammari N. Epidemiology and clinical presentation of pandemic influenza A (H1N1) among hospitalized children in Kuwait. Med Princ Pract. 2012;21(3):254-8.(111)	Design: Clinical case series (multi-centre) Period: August 2009–January 2010 Location: Kuwait	Case definition: Patient hospitalized with ILI and laboratory-confirmed influenza virus infection Presentation: ILI: axillary temperature of ≥38°C and cough and/or sore throat Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=197 hospitalized cases (n=6 [3.0%] ICU cases) Age group: Children Median age at hospitalization: 2 years (range: <0.1–12 years)	**Hospitalization** n=13 of 197 (6.6%) hospitalized cases had neurological disease, including seizures/epilepsy (n=5), cerebral palsy (n=6), and muscle disease (n=2) (n=88 [44.7%] hospitalized cases had underlying medical conditions). **ICU admission** n=4 of 6 (66.7%) ICU cases had seizure disorder (n=5 [83.3%] ICU cases had underlying medical conditions).	Level III n/a
Pebody RG, McLean E, Zhao H, et al. Pandemic Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Euro Surveill. 2010;15(20):19571.(112)	Design: Population case series Period: April 2009–March 2010 Location: UK (England)	Case definition: Death associated with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR Risk group definition: UK DH (includes chronic neurological disease and stroke/TIA)	Pandemic influenza A(H1N1)pdm09	n=336 fatal cases (n=308 [91.7%] fatal cases with available information on underlying health status) Age group: Predominantly adults Median age at death: 43 years (IQR: 24–57 years; n=48 of 308 [15.6%] fatal cases <16 years of age)	**Death** n=67 of 308 (21.8%) fatal cases had chronic neurological disease, including cerebral palsy/developmental delay (n=22), neuro-musculoskeletal disorders (n=10), epilepsy (n=9), and Down syndrome (n=7) (n=222 [72.1%] fatal cases had an underlying risk factor). **Death (6 months–64 years of age)** A much higher CFR (14.3, 95% CI: 5.3–38.3), population mortality rate (25.2 deaths per 100,000, 95% CI: 19.4–32.2), and PAF (24.3%) were observed among fatal cases with chronic neurological disease	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					compared to other underlying risk factors. A lower CFR (1.0, 95% CI: 0.1–5.9), population mortality rate (1.7 deaths per 100,000, 95% CI: 0.3–5.0), and PAF (0.8%) were observed among fatal cases with pre-existing stroke/TIA compared to other underlying risk factors. Individuals with pandemic influenza A(H1N1)pdm09 infection and chronic neurological disease (age-aRR: 115.3, 95% CI: 84.3–157.6) or pre-existing stroke/TIA (age-aRR: 7.5, 95% CI: 2.3–23.7) were at significantly higher risk of death compared to individuals with no underlying risk factors and without pandemic influenza A(H1N1)pdm09 infection. **Pandemic vs. seasonal (death)** The proportion with chronic neurological disease was not significantly different between fatal pandemic A(H1N1)pdm09 and seasonal influenza (death registry with an ICD-10 code for influenza [J09, J10, and J11] in England from January 2001–February 2009) cases.	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Pinilla I, de Gracia MM, Quintana-Díaz M, Figueira JC. Radiological prognostic factors in patients with pandemic H1N1 (pH1N1) infection requiring hospital admission. Emerg Radiol. 2011;18(4):313-9.(113)	Design: Clinical case series (single centre) Period: July–December 2009 Location: Spain	Case definition: Patient (>14 years of age) presented to the ED with ARI and laboratory-confirmed influenza virus infection Viral testing: RT-PCR and multiplex PCR to rule out other potential respiratory pathogens	Pandemic influenza A(H1N1)pdm09	n=104 ED cases (n=17 [16.3%] ICU cases) Age group: Predominantly adults Mean age at ED presentation: 40 years (range: 15–96 years) Mean age at ICU admission: 38 years (range: 17–71 years)	**ED presentation** n=1 of 104 (1.0%) ED cases had neurologic disease (n=43 [41.3%] ED cases had at least one co-existing medical condition). **ICU admission** n=1 of 17 (5.9%) ICU cases had neurologic disease (seizure disorder) (n=11 [64.7%] ICU cases had at least one co-existing medical condition).	Level III n/a
Poeppl W, Hell M, Herkner H, et al. Clinical aspects of 2009 pandemic influenza A (H1N1) virus infection in Austria. Infection. 2011;39(4):341-52.(114)	Design: Clinical case series (multi-centre) Period: September 2009–February 2010 Location: Austria	Case definition: Patient diagnosed with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR (n=516 of 540 [95.6%]) or RIDT	Pandemic influenza A(H1N1)pdm09	n=540 medically-attended cases (n=343 [63.5%] hospitalized cases, including 49 [14.3%] ICU cases) Age group: Predominantly adults Median age at ICU admission: 51.6 years (range: 0.3–85 years; n=8 of 49 [16.3%] ICU cases <18 years of age)	**ICU admission** n=9 of 49 (18.4%) ICU cases had neurological diseases (n=39 [79.6%] ICU cases had an underlying medical condition). Neurological comorbidity was significantly associated with ICU admission in medically-attended cases (aOR: 19.11, 95% CI: 3.92–93.22, p<0.001).	Level III n/a
Poulakou G, Souto J, Balcells J, et al. First influenza season after the 2009 pandemic influenza: characteristics of intensive care unit admissions in adults and children in Vall d'Hebron Hospital. Clin Microbiol Infect. 2012;18(4):374-80.(115)	Design: Clinical case series (single centre) Period: September 2009–January 2010 (pandemic) and September 2010–January	Case definition: Patient admitted to ICU for ARI with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR with multiplex RT-PCR used for subtyping	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2010–2011) n=21 of 23 (91.3%) seasonal ICU cases infected with influenza A	n=53 ICU cases (n=30 [56.6%] pandemic ICU cases and 23 [43.4%] seasonal ICU cases) Age group: Predominantly adults Median age at ICU admission: 37 years (IQR: 13.5–51.3 years; n=22 of 30 [73.3%] pandemic ICU cases >18 years of age) for	**ICU admission (pandemic)** n=1 of 30 (3.3%) pandemic ICU cases had neurological impairment (in children only) and 2 (6.7%) had neuromuscular disease (n=23 [76.7%] pandemic ICU cases had a comorbidity). **ICU admission (seasonal)** n=2 of 23 (8.7%) seasonal ICU cases had neurological impairment (in children only)	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
	2011 (seasonal) Location: Spain		and 2 (8.7%) with influenza B	pandemic cases and 29 years (IQR: 4.8–46 years; n=16 of 23 [69.6%] seasonal ICU cases >18 years of age) for seasonal cases	and 1 (4.3%) had neuromuscular disease (n=19 [82.6%] seasonal ICU cases had a comorbidity). **Pandemic vs. seasonal (ICU admission)** The proportion with neuromuscular impairment and neuromuscular disease were not significantly different between pandemic A(H1N1)pmd09 and seasonal A and B ICU cases (3.3% vs. 8.7%, p>0.20 and 6.7% vs. 4.3%, p>0.20, respectively).	
Prerna A, Lim JY, Tan NW, et al. Neurology of the H1N1 pandemic in Singapore: a nationwide case series of children and adults. J Neurovirol. 2015;21(5):491-9.[116]	Design: Population case series Period: May 2009–March 2010 Location: Singapore	Case definition: Patient hospitalized with ILI and laboratory-confirmed influenza virus infection and presented with neurologic symptoms, excluding those treated with neuraminidase inhibitors prior to the onset of neurological symptoms Presentation: ILI: fever (≥37.5°C) and at least one of the following: sore throat, cough, rhinorrhea, or nasal congestion) Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=98 hospitalized cases with neurologic symptoms Age group: Predominantly children Median age at hospitalization: 6.6 years (range: 0.4–62.6 years; n=88 of 98 [89.8%] hospitalized cases ≤18 years of age)	**Hospitalization** n=33 of 98 (33.7%) hospitalized cases had pre-existing neurologic disease, including epilepsy (n=13), history of febrile seizures (n=11), myasthenia gravis (n=2), Leigh's syndrome (n=2), chronic progressive external ophthalmoplegia (n=1), stroke (n=1), and previous syncope (n=1), as well as migraine (n=2; an excluded condition). **Post-infection (exacerbation)** n=2 of 2 (100.0%) hospitalized cases with pre-existing myasthenia gravis experienced exacerbation of their underlying condition (both adults).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Quach C, Piché-Walker L, Platt R, Moore D. Risk factors associated with severe influenza infections in childhood: implication for vaccine strategy. Pediatrics. 2003;112(3):e197-201.[117]	Design: Clinical case series (single centre) Period: April 1999–April 2002 Location: Canada	Case definition: Patient (children; age range not defined) presented to the ED with laboratory-confirmed influenza virus infection Viral testing: DFA (n=142 of 182 [78.0%] hospitalized cases) or viral culture, with findings from the latter test confirmed by DFA	Seasonal influenza A and B n=143 of 182 (78.6%) hospitalized cases infected with influenza A and 39 (21.4%) with influenza B	n=296 ED cases (n=182 [61.5%] hospitalized cases) Age group: Children Mean age at hospitalization (SD): 2.2 (3.4) years	**Hospitalization** n=9 of 182 (4.9%) hospitalized cases had a chronic neurologic disorder (n=55 [30.2%] hospitalized cases had an underlying illness).	Level III n/a
Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics. 2011;128(6):e1450-8.[118]	Design: Clinical case series (multi-centre) Period: April 2009–April 2010 Location: USA	Case definition: Patient (<21 years of age) admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR with subtype-specific primers or viral culture for confirmed cases (n=545 of 838 [65.0%]) or by DFA test or RIDT without further identification of subtype for probable cases (n=293 [35.0%])	Pandemic influenza A(H1N1)pdm09	n=838 ICU cases Age group: Predominantly children Median age at ICU admission: 6 years (n=808 of 838 [96.4%] ICU cases <18 years of age)	**ICU admission** n=263 of 838 (31.4%) ICU cases had neurologic or neuromuscular conditions (n=587 [70.0%] ICU cases had at least one underlying condition). **Death** Pre-existing neurologic condition was a significant predictor of mortality among ICU cases (RR: 1.8, 95% CI: 1.1–2.7, p=0.01).	Level III n/a
Rebolledo J, Igoe D, O'donnell J, et al. Influenza in hospitalized children in Ireland in the pandemic period and the 2010/2011 season: risk factors for paediatric intensive-care-unit admission. Epidemiol Infect.	Design: Population case series Period: April 2009–August 2010 (pandemic) and October 2010–May 2011	Case definition: Patient (≤14 years of age) hospitalized with ILI and laboratory-confirmed influenza virus infection Viral testing: Multiplex RT-PCR, with influenza A-positive samples further subtyped using RT-PCR. A small	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2010–2011) n=183 of 279 (65.6%) hospitalized	n=482 hospitalized pandemic cases and 279 hospitalized seasonal cases Age group: Children Median age at hospitalization: 5 years (range: 0–14 years) for pandemic cases and 2 years (range: 0–14 years) for	**Hospitalization (pandemic)** n=33 of 482 (6.8%) hospitalized pandemic cases had a neurological condition (n=154 of 458 [33.6%] had any medical condition). **Hospitalization (seasonal)** n=20 of 279 (7.2%) hospitalized seasonal cases had a neurological condition	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
2014;142(09):1826-35.[119]	(seasonal) Location: Ireland	proportion of influenza A-positive specimens were not subtyped (n=23 of 665 [3.4%])	seasonal cases infected with influenza A (n=160 [87.4%] subtyped: n=158 [98.8%] influenza A[H1N1]pdm09 and 2 [1.3%] influenza A[H3]) and 96 (34.4%) with influenza B	seasonal cases	(n=79 of 228 [34.6%] had any medical condition). **Pandemic vs. seasonal (hospitalization)** The proportion with neurological condition was not significantly different between hospitalized pandemic influenza A(H1N1)pdm09 and seasonal influenza A and B cases (6.8% vs. 7.2%, p=0.87). **ICU admission (pandemic)** Neurological condition was significantly associated with ICU admission among hospitalized cases in univariate analysis (RR: 13.65, 95% CI: 6.48–28.77, p<0.001), but was not significant in multivariate analysis. **ICU admission (seasonal)** Neurological condition was significantly associated with ICU admission among hospitalized cases in univariate analysis (RR: 3.8, 95% CI: 1.31–11.01, p=0.012) and multivariate (aRR: 6.07, 95% CI: 2.39–15.43, p<0.001) analyses.	
Reed C, Chaves SS, Perez A, et al. Complications among adults hospitalized with influenza: a	Design: Population case series Period:	Case definition: Patient (≥18 years of age) hospitalized with laboratory-confirmed influenza virus infection	Pandemic influenza A(H1N1)pdm09 Seasonal	n=4962 hospitalized pandemic cases and 5270 hospitalized seasonal cases Age group: Adults	**Hospitalization (pandemic)** n=466 of 4962 (9.4%) hospitalized pandemic cases had neurologic conditions, including neuromuscular	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
comparison of seasonal influenza and the 2009 H1N1 pandemic. Clin Infect Dis. 2014;59(2):166-74.(120)	October 2005–April 2009 (seasonal) and April 2009–April 2010 (pandemic) Location: USA	Viral testing: Direct or indirect fluorescent antibody staining, RIDT, RT-PCR, viral culture, or documentation of positive test in medical record	influenza A (2005–2006 through 2008–2009)	Median age at hospitalization: 47 years (IQR: 31–58 years) for pandemic cases and 68 years (IQR: 48–82 years) for seasonal cases	disease (n=217), seizure disorder (n=190), and cognitive dysfunction (n=204) (n=3957 [79.7%] hospitalized pandemic cases had underlying medical conditions). **Hospitalization (seasonal)** n=781 of 5270 (14.8%) hospitalized seasonal cases had neurologic conditions, including neuromuscular disease (n=278), seizure disorder (n=194), and cognitive dysfunction (n=450) (n=4431 [84.1%] hospitalized seasonal cases had underlying medical conditions). **Pandemic vs. seasonal (hospitalization)** The proportion with underlying neurologic conditions was significantly different between hospitalized pandemic influenza A(H1N1)pmd09 and seasonal influenza A cases (9.4% vs. 14.8%, p<0.01), including neuromuscular disease (4.4% vs. 5.3%, p=0.03) and cognitive dysfunction (4.1% vs. 8.5%, n<0.01), but not seizure disorder (3.8% vs. 3.7%, p=0.75).	
Regan J, Fowlkes A, Biggerstaff M, et al. Epidemiology of	Design: Population case series	Case definition: Death associated with laboratory-confirmed	Pandemic influenza A(H1N1)pdm09	n=302 fatal cases (n=297 [98.3%] fatal cases with available information on	**Death** n=62 of 297 (20.9%) fatal cases had a neurologic	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
influenza A (H1N1)pdm09-associated deaths in the United States, September-October 2009. Influenza Other Respir Viruses. 2012;6(6):e169-77.[121]	Period: September–October 2009 Location: USA	influenza virus infection Viral testing: DFA, RIDT, RT-PCR, or viral culture Risk group definition: ACIP		underlying health status) Age group: Predominantly adults (subgroup reporting for death outcome for children <18 years of age and adults ≥18 years of age) Median age at death: 45 years (range: <0.1–86 years; n=45 of 302 [14.9%] fatal cases <18 years of age)	disorder, including developmental delay (n=23), neuromuscular disorder (n=29), seizure disorder (n=27), and other neurologic disorders (n=30), and 10 (3.4%) had a history of stroke (n=214 [72.1%] fatal cases had an ACIP-defined high-risk underlying medical condition). **Death (<18 years of age)** n=15 of 43 (34.9%) fatal cases had a neurologic disorder, including developmental delay (n=13), neuromuscular disorder (n=8), seizure disorder (n=11), and other neurologic disorders (n=3), and 0 (0%) had a history of stroke (n=27 [62.8%] fatal cases had an ACIP-defined high-risk underlying medical condition). **Death (≥18 years of age)** n=47 of 254 (18.5%) fatal cases had a neurologic disorder, including developmental delay (n=10), neuromuscular disorder (n=21), seizure disorder (n=16), and other neurologic disorders (n=27), and 10 (3.9%) had a history of stroke (n=187 [73.6%] fatal cases had an ACIP-defined high-risk underlying medical condition).	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Rello J, Rodríguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care. 2009;13(5):R148.[122]	Design: Population case series Period: June–July 2009 Location: Spain	Case definition: Patient (≥15 years of age) admitted to ICU with severe respiratory failure and laboratory-confirmed influenza virus infection Presentation: Febrile (>38°C) acute illness and respiratory symptoms consistent with cough, sore throat, myalgia or ILI Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=32 ICU cases Age group: Predominantly adults Median age at ICU admission: 36 years (IQR: 31–52 years)	**ICU admission** n=1 of 32 (3.1%) ICU cases had neuromuscular disease (n=16 [50.0%] ICU cases had pre-existing medical complications).	Level III n/a
Riquelme R, Torres A, Rioseco ML, et al. Influenza pneumonia: a comparison between seasonal influenza virus and the H1N1 pandemic. Eur Respir J. 2011;38(1):106-11.[123]	Design: Clinical case series (multi-centre) Period: October 2003–December 2008 (seasonal) and May–July 2009 (pandemic) Location: Spain	Case definition: Patient (>16 years of age) hospitalized with radiologically-confirmed, community-acquired pneumonia and laboratory-confirmed influenza virus infection, excluding those who were non-immunocompetent Viral testing: Complement fixation test or haemagglutination test for seasonal influenza and RT-PCR for pandemic influenza	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A	n=127 hospitalized pandemic and seasonal cases with pneumonia (n=75 [59.1%] hospitalized pandemic cases and 52 [40.9%] hospitalized seasonal cases) Age group: Predominantly adults Mean age at hospitalization (SD): 39.7 (16.7) years for pandemic cases and 69.6 (17.0) years for seasonal cases	**Hospitalization with pneumonia (pandemic)** n=3 of 75 (4.0%) hospitalized pandemic cases with pneumonia had a neurological disorder. **Hospitalization with pneumonia (seasonal)** n=11 of 52 (21.2%) hospitalized seasonal cases with pneumonia had a neurological disorder. **Pandemic vs. seasonal (hospitalization with pneumonia)** The proportion with neurological disorders was significantly different between hospitalized pandemic influenza A(H1N1)pmd09 and seasonal influenza A cases with pneumonia (4.0% vs. 21.2%, p=0.002).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Rodríguez-Rieiro C, Carrasco-Garrido P, Hernández-Barrera V, et al. Pandemic influenza hospitalization in Spain (2009): Incidence, in-hospital mortality, comorbidities and costs. Hum Vaccin Immunother. 2012;8(4):443-7.[124]	Design: Population case series Period: July–December 2009 Location: Spain	Case definition: Patient hospitalized with influenza virus infection (ICD-9-CM code: 488.1) corresponding to laboratory-confirmed pandemic influenza Viral testing: Specific methods NR Risk group definition: Spain Ministry for Health (includes hereditary and degenerative diseases of the CNS [ICD-9-CM codes: 330.x–337.x] and epilepsy [345.x])	Pandemic influenza A(H1N1)pdm09	n=11,449 hospitalized cases (n=282 [2.5%] fatal cases) Age group: Predominantly adults Median age at hospitalization: 34 years (IQR: 51 years; n=2901 of 11,449 [25.3%] hospitalized cases <14 years of age)	**Hospitalization** n=257 of 11,449 (2.2%) hospitalized cases had epilepsy and 119 (1.0%) had hereditary and degenerative diseases of the CNS (n=5791 [50.6%] hospitalized cases had an underlying chronic disease). **Hospitalization (<15 years of age)** n=98 of 2901 (3.4%) hospitalized cases had epilepsy and 23 (0.8%) had hereditary and degenerative diseases of the CNS. **Hospitalization (≥15 years of age)** n=159 of 8548 (1.9%) hospitalized cases had epilepsy and 96 (1.1%) had hereditary and degenerative diseases of the CNS. **Death** n=15 of 282 (5.3%) fatal cases had epilepsy and 15 (5.3%) had hereditary and degenerative diseases of the CNS. **Death (<15 years of age)** n=7 of 23 (30.4%) fatal cases had epilepsy and 3 (13.0%) had hereditary and degenerative diseases of the CNS.	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Death (≥15 years of age) n=8 of 259 (3.1%) fatal cases had epilepsy and 12 (4.6%) had hereditary and degenerative diseases of the CNS.	
Rosen DG, Lopez AE, Anzalone ML, et al. Postmortem findings in eight cases of influenza A/H1N1. Mod Pathol. 2010;23(11):1449-57.(125)	Design: Clinical case series (single centre) Period: June–September 2009 Location: USA	Case definition: Death associated with laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=8 fatal cases Age group: Predominantly adults Median age at death: 27 years (range: 0.5–54 years; n=1 of 8 [12.5%] fatal cases <18 years of age)	**Death** n=2 of 8 (25.0%) fatal cases had a neurologic condition, including a history of mental retardation (n=1) or MG (n=1) (n=5 [62.5%] fatal cases had comorbid conditions).	Level III n/a
Sam IC, Abdul-Murad A, Karunakaran R, et al. Clinical features of Malaysian children hospitalized with community-acquired seasonal influenza. Int J Infect Dis. 2010;14:e36-40.(126)	Design: Clinical case series (single centre) Period: 2002–2007 Location: Malaysia	Case definition: Patient (<15 years of age) hospitalized with community-acquired, laboratory-confirmed influenza virus infection Viral testing: Immunofluorescence or virus isolation Risk group definition: ACIP	Seasonal influenza A and B n=97 of 132 (73.5%) hospitalized cases infected with influenza A and 35 (26.5%) with influenza B	n=132 hospitalized cases Age group: Children Mean age at hospitalization (SD): 2.5 (2.9) years	**Hospitalization** n=7 of 132 (5.3%) hospitalized cases had neurological or neuromuscular disorders (n=48 [36.4%] hospitalized cases had an ACIP-defined high-risk chronic medical condition).	Level III n/a
Santa-Olalla Peralta P, Cortes-García M, Vicente-Herrero M, Castrillo-Villamandos C, et al. Risk factors for disease severity among hospitalised patients with 2009 pandemic influenza A (H1N1) in Spain, April - December 2009. Euro	Design: Population case series Period: April–December 2009 Location: Spain	Case definition: Patient hospitalized with laboratory-confirmed influenza virus infection (a severe case was defined as those who were admitted to ICU or died) Viral testing: Subtype-specific RT-PCR	Pandemic influenza A(H1N1)pdm09	n=3025 hospitalized cases (n=891 [29.5%] ICU or fatal cases, including 852 [28.2%] ICU cases and 200 [6.6%] fatal cases; n=2508 [82.9%] hospitalized cases with available information on underlying health status) Age group: Predominantly adults (subgroup reporting	**Hospitalization** n=137 of 1913 (7.2%) hospitalized cases had cognitive dysfunction, 102 of 2324 (4.4%) had seizures, and 83 of 1887 (4.4%) had neuromuscular disease (73.6% of hospitalized cases had at least one underlying risk condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Surveill. 2010;15(38).[127]				for hospitalization outcome for children <15 years of age and adults ≥15 years of age) Median age at hospitalization: 37 years (range: 0–94 years; n=605 of 3025 [20.0%] hospitalized cases <15 years of age) Median age at ICU admission or death: 41 years (range 0–92) (n=131 of 852 [15.4%] ICU cases <15 years of age)	**Hospitalization (<15 years of age)** n=35 of 358 (9.8%) hospitalized cases had cognitive dysfunction, 40 of 446 (9.0%) had seizures, and 28 of 364 (7.7%) had neuromuscular disease (60.8% of hospitalized cases had at least one underlying risk condition). **Hospitalization (≥15 years of age)** n=102 of 1554 (6.6%) hospitalized cases had cognitive dysfunction, 62 of 1877 (3.3%) had seizures, and 55 of 1522 (3.6%) had neuromuscular disease (76.5% of hospitalized cases had at least one underlying risk condition). **ICU admission or death** n=57 of 640 (8.9%) ICU or fatal cases had cognitive dysfunction, 49 of 751 (6.5%) had seizures, and 31 of 627 (4.9%) had neuromuscular disease (73.2% of ICU or fatal cases had an underlying risk condition). Cognitive disorder and seizure were significantly associated with ICU admission or death (p=0.029 and 0.001, respectively), but not neuromuscular disease (p=0.407) among	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					hospitalized cases in univariate analysis. All three neurologic conditions were not significantly associated with ICU admission or death in multivariate analysis in adult hospitalized cases.	
Sasbón JS, Centeno MA, García MD, et al. Influenza A (pH1N1) infection in children admitted to a pediatric intensive care unit: differences with other respiratory viruses. Pediatr Crit Care Med. 2011;12(3):e136-40.(128)	Design: Clinical case series (single centre) Period: June–July 2008 (other respiratory viruses) and June–July 2009 (pandemic) Location: Argentina	Case definition: Patient (≥1 month of age) admitted to ICU with acute lower respiratory tract infection and laboratory-confirmed respiratory virus infection, including influenza Viral testing: Indirect immunofluorescence antibody testing with subtype confirmed by rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=30 pandemic ICU cases and 62 ICU cases with other respiratory viruses (no subgroup reporting for seasonal influenza viruses) Age group: Children Median age at ICU admission for pandemic cases: 2.5 years (range: 0.1–17.9 years)	**ICU admission** n=9 of 30 (30.0%) pandemic ICU cases had an underlying neurological condition (n=25 [83.3%] pandemic ICU cases had an underlying condition).	Level III n/a
Schrag SJ, Shay DK, Gershman K, et al. Multistate surveillance for laboratory-confirmed, influenza-associated hospitalizations in children: 2003–2004. Pediatr Infect Dis J. 2006;25(5):395-400.(129)	Design: Population case series Period: October 2003–March 2004 Location: USA (nine states)	Case definition: Patient (<18 years of age) hospitalized with community-acquired, laboratory-confirmed influenza virus infection Viral testing: RIDT (70%), DFA (14%), multiple test types (10%), viral culture (3%), RT-PCR (0.2%), and unknown test type (3%) Risk group definition: ACIP (before inclusion of neurologic disease in	Seasonal influenza (2003–2004)	n=1308 hospitalized cases Age group: Children	**Hospitalization** n=68 of 1308 (5.2%) hospitalized cases had neuromuscular or cognitive disorders, including developmental delay, spinal cord injuries or other forms of paralysis, cerebral palsy, and autism (n=339 [25.9%] of hospitalized cases had at least one ACIP-defined high-risk medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		children)				
Scotta MC, Mattiello R, Marostica PJ, Jones MH, Martins LG, Fischer GB. Risk factors for need of mechanical ventilation in children with influenza A(H1N1)pdm09. J Pediatr (Rio J). 2013;89(5):444-9.(130)	Design: Population case series Period: July–October 2009 Location: Brazil (Porto Alegre)	Case definition: Patient (<14 years of age) hospitalized with ILI and laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=120 hospitalized cases (n=11 [9.2%] fatal cases) Age group: Children Median age at hospitalization: 1.5 years (IQR: 0.4–5.6 years)	**Hospitalization** n=17 of 120 (14.2%) hospitalized cases had neurologic impairment (n=52 [43.3%] hospitalized cases had chronic disease). **Death** n=5 of 11 (45.5%) fatal cases had neurologic impairment (n=10 [90.9%] fatal cases had chronic disease).	Level III n/a
Sharma R, Agarwal S, Mehta S, et al. Profiling the Mortality due to Influenza A (H1N1) pdm09 at a Tertiary Care Hospital in Jaipur during the Current Season--January & February 2015. J Assoc Physicians India. 2015;63(4):36-9.(131)	Design: Clinical case series (single centre) Period: January–February 2015 Location: India	Case definition: Death associated with laboratory-confirmed influenza virus infection requiring hospitalization Viral testing: RT-PCR	Seasonal (post-pandemic) influenza A(H1N1)pdm09	n=76 fatal cases Age group: Adults Mean age at death (SD): 44.01 (15.07) years *(n=76 of 76 [100.0%] fatal cases ≥18 years of age)*	**Death** n=2 of 76 (2.6%) fatal cases had pre-existing stroke (n=49 [64.5%] fatal cases had one or more comorbid condition).	Level III n/a
Shin SY, Kim JH, Kim HS, et al. Clinical characteristics of Korean pediatric patients critically ill with influenza A (H1N1) virus. Pediatr Pulmonol. 2010;45(10):1014-20.(132)	Design: Population case series Period: June–November 2009 Location: South Korea	Case definition: Patient (≤18 years of age) admitted to ICU or required mechanical ventilation for pneumonia with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR Risk group definition: ACIP	Pandemic influenza A(H1N1)pdm09	n=30 ICU or mechanically ventilated cases Age group: Children Median age at ICU admission or mechanical ventilation: 7 years (range: 0.2–18 years)	**ICU admission or mechanical ventilation** n=4 of 30 (13.3%) ICU or mechanically ventilated cases had neurological disease, including neurodevelopmental disorder (n=2) and seizure (n=2) (n=19 [63.3%] ICU or mechanically ventilated cases had an ACIP-defined high-risk condition)	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Sibley WA, Bamford CR, Laguna JF. Influenza vaccination in patients with multiple sclerosis. JAMA. 1976;236(17):1965-6.[133]	Design: Clinical case series (single centre) Period: 1962–1975 (immunization) Location: USA	Case definition: Patient with well-documented MS Vaccination status: Medical records with confirmation by interview	Seasonal influenza vaccine	n=93 MS patients Age group: Predominantly adults (assumed; age range NR)	**Post-vaccination (exacerbation)** n=1 of 93 MS patients showed evidence of a new lesion (i.e., exacerbation of MS) in the one month following influenza vaccination; the observed relapse rate of 0.6 attacks per patient per year was less than would be expected in the natural course of the illness. The authors noted that the single observed exacerbation was likely due to chance rather than being secondary to the influenza vaccine.	Level III n/a
Skarbinski J, Jain S, Bramley A, et al. Hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in the United States--September-October 2009. Clin Infect Dis. 2011;52 Suppl 1:S50-9.[134]	Design: Population case series Period: September–October 2009 Location: USA	Case definition: Patient hospitalized with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=255 hospitalized cases (n=89 [34.9%] ICU or fatal cases) Age group: Predominantly adults (subgroup reporting for hospitalization outcome for children <18 years of age and adults ≥18 years of age) Median age at hospitalization: 28 years (range: <0.1–87 years; n=86 of 255 [33.7%] hospitalized cases <18 years of age) Median age at ICU admission or death: 32 years (range: 0.8–70 years)	**Hospitalization** n=17 of 255 (6.7%) hospitalized cases had a neurocognitive disorder, 19 (7.5%) had a neuromuscular disorder, and 14 (5.5%) had a seizure disorder (n=170 [66.7%] hospitalized cases had an underlying medical condition). **Hospitalization (<18 years of age)** 14% of 86 hospitalized cases had neurologic disorders, including neurocognitive disorder (n=7), neuromuscular disorder (n=8), and seizure disorder (n=6) (n=41 [47.7%] hospitalized cases had an underlying medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					Hospitalization (≥18 years of age) 14% of 169 hospitalized cases had neurologic disorders, including neurocognitive disorder (n=10), neuromuscular disorder (n=11), and seizure disorder (n=8) (n=129 [76.3%] hospitalized cases had an underlying medical condition). **ICU admission or death** n=9 of 89 (10.1%) ICU or fatal cases had a neurocognitive disorder, 9 (10.1%) had a neuromuscular disorder, and 7 (7.9%) had a seizure disorder (n=56 [62.9%] ICU or fatal cases had an underlying medical condition).	
Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004;351(25):2611-8.[135]	Design: Population self-controlled case series Period: 1987–2001 Location: UK	Case definition: Patient (≥18 years of age at the time of a first myocardial infarction or stroke recorded in registry) registered for at least one year with a general practice that contributed to the registry and had received one or two new diagnoses of myocardial infarction or stroke during the period of at least six months after the start of their follow-up in the registry, excluding those with vascular	Seasonal influenza vaccine	n=4139 patients with a second stroke and at least one influenza vaccination Age group: Adults	**Post-vaccination (recurrence)** Incidence rate of recurrent stroke was significantly lower in risk periods (1–91 days post-vaccination) compared to baseline periods (1–3 days post-vaccination: n=19 cases, age-adjusted IR: 0.56, 95% CI: 0.35–0.89; 4–7 days: n=33 cases, age-adjusted IR: 0.74, 95% CI: 0.52–1.05; 8–14 days: n=56, age-adjusted IR: 0.72, 95% CI: 0.55–0.94; 15–28 days: n=105, age-adjusted IR: 0.69, 95% CI: 0.57–0.85; 29–	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		events likely to have been recorded retrospectively Influenza vaccination status: Registry record			91 days: n=516, age-adjusted IR: 0.79, 95% CI: 0.71–0.87; baseline period: n=3396 cases).	
Stein M, Tasher D, Glikman D, et al. Hospitalization of children with influenza A(H1N1) virus in Israel during the 2009 outbreak in Israel: a multicenter survey. Arch Pediatr Adolesc Med. 2010;164(11):1015-22.[136]	Design: Population case series Period: July–December 2009 Location: Israel	Case definition: Patient (≤18 years of age) hospitalized with ARI or acute unspecified febrile illness and laboratory-confirmed influenza virus infection Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=478 hospitalized cases (n=42 [8.8%] ICU cases) Age group: Predominantly children Mean age at hospitalization: 6.1 years (range: 0.03–18 years)	**Hospitalization** n=41 of 478 (8.6%) hospitalized cases had predisposing neurologic illness (n=233 [48.7%] hospitalized cases had any predisposing illness). **ICU admission** n=8 of 42 (19.0%) ICU cases had predisposing neurologic illness (n=27 [64.3%] ICU cases had predisposing illness). Neurologic disorder was significantly associated with ICU admission among hospitalized cases (RR: 2.9, 95% CI: 1.3–6.6, p=0.02).	Level III n/a
Streng A, Prifert C, Weissbrich B, et al. Continued high incidence of children with severe influenza A(H1N1)pdm09 admitted to paediatric intensive care units in Germany during the first three post-pandemic influenza seasons, 2010/11-2012/13. BMC Infect Dis. 2015;15:573. [137]	Design: Population case series Period: October 2010–September 2013 Location: Germany (Bavaria)	Case definition: Patient (1 month–16 years of age) admitted to ICU with ARI and laboratory-confirmed influenza virus infection Presentation: ARI-related symptoms: coryza, cough, or sore throat Viral testing: Multiplex (n=41 of 51 [80.4%]) or	Seasonal influenza A and B (2010–2011 through 2012–2013) n=40 of 47 (85.1%) ICU cases infected with influenza A (n=36 [90.0%] subtyped: n=32 [88.9%] influenza	n=51 ICU cases (n=47 [92.2%] ICU cases with available information on underlying health status; n=5 of 47 [10.6%] fatal ICU cases) Age group: Children Median age at ICU admission: 4.8 years (IQR: 1.6–11.0 years)	**ICU admission** n=16 of 47 (34.0%) ICU cases had neurologic disease (n=36 [76.6%] ICU cases had at least one medical condition). **ICU death** n=4 of 5 (80.0%) fatal ICU cases had neurologic disease (n=5 [100.0%] fatal ICU cases had at least one medical condition).	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
		singleplex (n=10 [19.6%]) RT-PCR	A[H1N1]pdm09 and 4 [11.1%] influenza A[H3N]) and 7 (14.9%) with influenza B			
Streng A, Grote V, Liese JG. Severe influenza cases in paediatric intensive care units in Germany during the pre-pandemic seasons 2005 to 2008. BMC Infect Dis. 2011;11:233.(138)	Design: Population case series Period: October 2005–July 2008 Location: Germany	Case definition: Patient (<17 years of age) admitted to ICU with laboratory-confirmed influenza virus infection Viral testing: Antigen test, RT-PCR, or virus isolate	Seasonal influenza A and B (2005–2006 through 2007–2008) n=14 of 20 (70.0%) ICU cases infected with influenza A, 5 (25.0%) with influenza B, and 1 (5.0%) with type undetermined	n=20 ICU cases Age group: Children Median age at ICU admission: 7.5 years (range: 0.1–15 years)	**ICU admission** n=2 of 20 (10.0%) ICU cases had an underlying neurologic condition, including hereditary motor and sensory neuropathy, and unclear retardation (n=11 [55.0%] ICU cases had underlying chronic medical conditions).	Level III n/a
Subramony H, Lai FY, Ang LW, Cutter JL, Lim PL, James L. An epidemiological study of 1348 cases of pandemic H1N1 influenza admitted to Singapore Hospitals from July to September 2009. Ann Acad Med Singapore. 2010;39(4):283.(139) *(Supplemented with additional details from Cutter JL et al. Ann Acad Med Singapore. 2010;39(4):273-10.(153) [Subgroup reporting of*	Design: Population case series Period: July–September 2009 Location: Singapore	Case definition: Patient hospitalized with laboratory-confirmed influenza virus infection, excluding those admitted for reasons of quarantine Viral testing: RT-PCR	Pandemic influenza A(H1N1)pdm09	n=1348 hospitalized cases (n=92 [6.8%] ICU or fatal cases, including 18 fatal cases with 4 fatal cases not admitted to ICU) Age group: Mixture of children and adults (hospitalization); predominantly adults (ICU admission or death; death) (subgroup reporting for hospitalization, ICU admission or death, and death outcomes for children <20 years of age and adults ≥20 years of age) Median age at	**Hospitalization** n=21 of 1348 (1.6%) hospitalized cases had cerebrovascular diseases, 27 (2.0%) had epilepsy, and 12 (0.9%) had neuromuscular disorders (n=679 [50.4%] hospitalized cases had one or more underlying medical conditions). **Hospitalization (<20 years of age)** n=18 of 543 (3.3%) hospitalized cases had epilepsy and 6 (1.1%) had neuromuscular disorder (n=281 [51.7%] hospitalized cases had at least one risk	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
hospitalized, ICU or fatal, and fatal cases for children <20 years of age and adults ≥20 years of age]).				hospitalization: 25 years (IQR: 12–50 years; n=543 pf 1348 [40.3%] hospitalized cases <20 years) Median age at ICU admission and/or death: 44 years (IQR: 23.5–53.5 years; n=16 of 92 [17.4%] ICU or fatal cases <20 years) Median age at death: 50 years (IQR: 36–68 years)	factor). **Hospitalization (≥20 years of age)** n=9 of 805 (1.1%) hospitalized cases had epilepsy and 6 (0.7%) had neuromuscular disorder (n=506 [62.9%] hospitalized cases had at least one risk factor). **ICU admission or death** n=4 of 92 (4.3%) ICU or fatal cases had cerebrovascular diseases, 7 (7.6%) had epilepsy, and 7 (7.6%) had neuromuscular disorders, including MG (n=1), Duchenne muscular dystrophy (n=1), neurodevelopmental delay (n=1), Parkinson's disease (n=1), Leigh's syndrome (n=2), and amyotrophic lateral sclerosis (n=1) (n=66 [71.7%] ICU or fatal cases had one or more underlying medical conditions). Epilepsy and neuromuscular disorders were significant predictors of severe illness (admission to ICU and/or death) among hospitalized cases (aOR: 6.22, 95% CI: 2.29–16.90, p=0.0003 and aOR: 17.81, 95% CI: 4.97–63.85, p<0.0001, respectively). Cerebrovascular disease	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					was not significantly associated with severe illness among hospitalized cases (aOR: 1.69, 95% CI: 0.45–6.36, p=0.4350). **ICU admission or death (<20 years of age)** n=7 of 16 (43.8%) ICU or fatal cases had epilepsy and 3 (18.8%) had neuromuscular disorder (n=12 [75.0%] ICU or fatal cases had at least one risk factor). **ICU admission or death (≥20 years of age)** n=0 of 76 (0%) ICU or fatal cases had epilepsy and 4 (5.3%) had neuromuscular disorder (n=53 [69.7%] ICU or fatal cases had at least one risk factor). **Death** n=2 of 18 (11.1%) fatal cases had neuromuscular disease, including Parkinson's disease (n=1) and amyotrophic lateral sclerosis (n=1) (n=14 [22.2%] fatal cases had one or more underlying medical conditions). **Death (<20 years of age)** n=1 of 2 (50.0%) fatal cases had epilepsy and 0 (0%) had neuromuscular disorder (n=2 [100.0%] fatal cases had at	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					least one risk factor). **Death (≥20 years of age)** n=0 of 16 (0%) fatal cases had epilepsy and 2 (12.5%) had neuromuscular disorder (n=12 [75.0%] fatal cases had at least one risk factor).	
Tamma PD, Turnbull AE, Milstone AM, et al. Clinical outcomes of seasonal influenza and pandemic influenza A (H1N1) in pediatric inpatients. BMC Pediatr. 2010;10:72.(140)	Design: Clinical case series (single centre) Period: 2007–2009 (seasonal) and May–December 2009 (pandemic) Location: USA	Case definition: Patient (≤18 years of age) hospitalized with ILI and laboratory-confirmed influenza virus infection Presentation: ILI: fever and upper respiratory tract symptoms (cough, sore throat, rhinorrhea, congestion), lower respiratory symptoms (wheezing, chest pain, shortness of breath), or gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) Viral testing: DFA (n=39 of 133 [29.3%]) or viral culture (n=94 [70.7%]), with rtRT-PCR subtype confirmation, for pandemic influenza and RIDT (n=55 of 133 [41.4%]) for seasonal influenza, with negative samples further tested by DFA and viral culture	Pandemic influenza A(H1N1)pdm09 Seasonal influenza A and B (2007–2008 and 2008–2009)	n=133 hospitalized pandemic cases and 133 hospitalized seasonal cases Age group: Children Mean age at hospitalization (SD): 7.3 (5.4) years for pandemic cases and 7.0 (5.7) years for seasonal cases	**Hospitalization (pandemic)** n=9 of 133 (6.8%) hospitalized pandemic cases had neuromuscular disorder (n=109 [82.0%] hospitalized pandemic cases had pre-existing medical conditions). **Hospitalization (seasonal)** n=24 of 133 (18.0%) hospitalized seasonal cases had neuromuscular disorder (n=98 [73.7%] hospitalized seasonal cases had pre-existing medical conditions). **Pandemic vs. seasonal (hospitalization)** The proportion with neuromuscular disorder was significantly different between hospitalized pandemic influenza A(H1N1)pdm09 and seasonal influenza A and B cases (6.8% vs. 18.0%, p<0.01).	Level III n/a
Thompson DL, Jungk J, Hancock E, et al. Risk factors for 2009	Design: Population case series	Case definition: Patient hospitalized with laboratory-confirmed	Pandemic influenza A(H1N1)pdm09	n=926 hospitalized cases (n=106 [11.4%] mechanically ventilated cases and 35	**Hospitalization** n=103 of 926 (11.1%) hospitalized cases had	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
pandemic influenza A (H1N1)–related hospitalization and death among racial/ethnic groups in New Mexico. Am J Public Health. 2011;101(9):1776-84.(141)	Period: September 2009–January 2010 Location: USA (New Mexico)	influenza virus infection Viral testing: Direct or indirect fluorescent antibody, RIDT, viral culture, or rtRT-PCR		[3.8%] fatal cases) Age group: Mixture of children and adults Age at hospitalization: n=445 of 926 (48.1%) hospitalized cases <25 years of age	neurological disease (n=575 [62.1%] hospitalized cases had any high-risk medical condition). **Mechanical ventilation** n=19 of 106 (17.9%) mechanically ventilated cases had neurological disease (n=74 [69.8%] mechanically ventilated cases had any high-risk medical condition). Neurological disease was significantly associated with mechanical ventilation among hospitalized cases in univariate analysis (OR: 1.9, 95% CI: 1.1–3.3), but not in multivariate analysis (aOR: 1.5, 95% CI: 0.7–3.2 [with obesity as covariate] or aOR: 1.3, 95% CI: 0.6–2.9 [without obesity as covariate]). **Death** n=7 of 35 (20.0%) fatal cases had neurological disease (n=27 [77.1%] fatal cases had any high-risk medical condition). Neurological disease was not significantly associated with death among hospitalized cases (OR: 2.0, 95% CI: 0.8–4.7).	
Tokuhira N, Shime N, Inoue M, et al. Mechanically ventilated	Design: Clinical case series (multi-	Case definition: Patient (<17 years of age) admitted to ICU requiring	Pandemic influenza A(H1N1)pdm09	n=81 ICU cases Age group: Children	**ICU admission** n=10 of 81 (12.3%) ICU cases had neurological	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
children with 2009 pandemic influenza A/H1N1: results from the National Pediatric Intensive Care Registry in Japan. Pediatr Crit Care Med. 2012;13(5):e294-8.(142)	centre) Period: July 2009–March 2010 Location: Japan	mechanical ventilation with laboratory-confirmed or probable influenza virus infection Viral testing: n=74 of 81 (91.4%) cases had laboratory confirmation: RT-PCR (n=60 of 81 [74.1%]), RIDT (n=14 [17.3%]), or clinical diagnosis only (n=7 [8.6%])		Median age at ICU admission: 6.3 years (IQR: 4.4–9 years)	disease (n=41 [50.6%] ICU cases had at least one underlying chronic condition).	
Törün SH, Karakılıç E, Aktürk H, et al. Influenza in the pediatric population in Istanbul: a one center experience 2009-2014. Epidemiol Mikrobiol Imunol. 2016;65(1):46-50.(143)	Design: Clinical case series (single centre) Period: October 2009–May 2014 Location: Turkey (Istanbul)	Case definition: Patient (≤18 years of age) hospitalized with laboratory-confirmed influenza virus infection Viral testing: rtRT-PCR	Seasonal influenza A and B and pandemic influenza A(H1N1)pdm09 (2009–2010 through 2013–2014, including pandemic influenza season) n=133 of 230 (57.8%) hospitalized cases infected with influenza A(H1N1), 53 (23.0%) with influenza A(H3N2), and 44 (19.1%) with influenza B	n=230 hospitalized cases Age group: Children Mean age at hospitalization (SD): 5.5 (4.4) years (range: <0.1–17 years)	**Hospitalization** 8.6% of 230 hospitalized cases had underlying neurological disorders (n=124 [53.9%] hospitalized cases had underlying chronic disease).	Level III n/a
Tran D, Vaudry W, Moore DL, et al. Comparison of children hospitalized with	Design: Clinical case series (multi-centre)	Case definition: Patient (≤16 years of age) hospitalized with laboratory-confirmed	Pandemic influenza A(H1N1)pdm09	n=1265 hospitalized pandemic cases (n=185 [14.6%] pandemic ICU cases) and 1319	**Hospitalization (pandemic)** n=172 of 1265 (13.6%) hospitalized pandemic cases had a neurologic condition	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
seasonal versus pandemic influenza A, 2004-2009. Pediatrics. 2012;130(3):397-406.(144) *(Dataset overlaps with Burton C, et al. Pediatr Infect Dis J. 2014;33(7):710-4.(6) [Hospitalized seasonal cases])*	Period: September 2004–March 2009 (seasonal) and May 2009–March 2010 (pandemic) Location: Canada	influenza virus infection Viral testing: DFA assay, RT-PCR, and/or viral culture, with all pandemic cases subtyped by RT-PCR specific for A(H1N1)pdm09 (DFA- or culture-positive, but A(H1N1)pdm09-negative patients were excluded)	Seasonal influenza A (2004–2005 through 2008–2009)	hospitalized seasonal cases (n=167 [12.7%] seasonal ICU cases) Age group: Children Median age at hospitalization: 4.8 years (IQR: 1.6–8.9 years) for pandemic cases and 1.7 years (IQR: 0.6–4.8 years) for seasonal cases Median age at ICU admission: 6.0 years (IQR: 2.1–9.8 years) for pandemic cases and 2.0 years (IQR: 0.9–4.8 years) for seasonal cases	(n=743 [58.7%] hospitalized pandemic cases had an underlying medical condition). **Hospitalization (seasonal)** n=140 of 1319 (10.6%) hospitalized seasonal cases had a neurologic condition (n=659 [50.0%] hospitalized seasonal cases had an underlying medical condition). **ICU admission (pandemic)** n=37 of 185 (20.0%) pandemic ICU cases had a neurologic condition (n=127 [68.6%] pandemic ICU cases had an underlying medical condition). Neurologic condition was a significant predictor of ICU admission among hospitalized pandemic influenza A(H1N1)pdm09 cases in multivariate models without ethnic origin included as a covariate (aOR: 2.11, 95% CI: 1.32–3.38, p=0.002) and remained significant when additionally adjusted for ethnic origin (aOR: 1.93, 95% CI: 1.05–3.55, p=0.04). **ICU admission (seasonal)** n=39 of 167 (23.4%) seasonal ICU cases had a neurologic condition (n=97 [58.1%] seasonal ICU cases	

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
					had an underlying medical condition). Neurologic condition was a significant predictor of ICU admission among hospitalized seasonal influenza A cases in multivariate models without ethnic origin included as a covariate (aOR: 4.30, 95% CI: 2.57–7.21, p<0.0001), but was not significant when additionally adjusted for ethnic origin (aOR: 1.87, 95% CI: 0.25–14.14, p=0.55). **Pandemic vs. seasonal (hospitalization)** Hospitalized pandemic influenza A(H1N1)pdm09 cases had similar age-adjusted odds of having an underlying neurologic condition compared to seasonal influenza A cases (age-aOR: 1.07, 95% CI: 0.83–1.37, p=0.60). The proportion with underlying neurologic condition was not significantly different between pandemic influenza A(H1N1)pdm09 and seasonal influenza A cases (20.0% vs. 23.4%, p=0.45).	
Tresoldi AT, Pereira RM, Fraga AM, et al. Clinical features and	Design: Clinical case series (multi-	Case definition: Patient (children; age range not defined) hospitalized	Pandemic influenza A(H1N1)pdm09	n=61 hospitalized cases with acute respiratory distress, including 15 hospitalized	**ICU admission** n=2 of 7 (28.6%) ICU cases had chronic neuropathy (n=6	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
outcome of children and adolescents hospitalized with influenza A (H1N1) virus infection compared with flu-like symptoms and negative rapid tests for influenza A (H1N1) admitted in the same period of time. J Trop Pediatr. 2011;57(6):481-3.(145)	centre) Period: July–August 2009 Location: Brazil	with febrile or non-febrile acute respiratory distress Viral testing: RT-PCR		pandemic cases (n=7 of 15 [46.7%] pandemic ICU cases) Age group: Children Median age at ICU admission: 2 years (range: 0.3–16 years)	[85.7%] ICU cases had comorbidities).	
Uchimura T, Mori M, Nariai A, Yokota S. Analysis of cases of severe respiratory failure in children with influenza (H1N1) 2009 infection in Japan. J Infect Chemother. 2012;18(1):59-65.(146)	Design: Population case series Period: August–December 2009 Location: Japan	Case definition: Patient (children; age range not defined) hospitalized with laboratory-confirmed influenza virus infection and severe respiratory failure requiring mechanical ventilation Viral testing: rtRT-PCR	Pandemic influenza A(H1N1)pdm09	n=31 hospitalized cases with severe respiratory failure Age group: Children Median age at hospitalization: 7 years (range: 0.9–10 years)	**Hospitalization with severe respiratory failure** n=3 of 31 (9.7%) hospitalized cases had mental retardation and 1 (3.2%) had a history of epilepsy.	Level III n/a
Weigl JA, Puppe W, Schmitt HJ. The incidence of influenza-associated hospitalizations in children in Germany. Epidemiol Infect. 2002;129(3):525-33.(147)	Design: Clinical case series (multi-centre) Period: July 1996–June 2001 Location: Germany	Case definition: Patient (<17 years of age) hospitalized with ARI and community-acquired, laboratory-confirmed respiratory virus infection, including influenza Viral testing: Multiplex RT-PCR	Seasonal influenza A and B (1996–1997 through 2000–2001) n=122 of 136 (89.7%) hospitalized seasonal cases infected with influenza A and 14 (10.3%) with influenza B	n=136 hospitalized seasonal cases (community-acquired and nosocomial) n=116 hospitalized community acquired seasonal cases Age group: Children	**Hospitalization** n=4 of 116 (3.4%) hospitalized cases had a neurological condition (n=24 [20.7%] hospitalized cases had an underlying condition).	Level III n/a
Wie SH, So BH, Song JY, et al. A comparison	Design: Clinical case	Case definition: Patient presented to the ED with	Seasonal influenza A and	n=850 ED cases (n=79 [9.3%] hospitalized cases)	**ED presentation** n=32 of 850 (3.8%) ED	Level III

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
of the clinical and epidemiological characteristics of adult patients with laboratory-confirmed influenza A or B during the 2011–2012 influenza season in Korea: a multi-center study. PLoS One. 2013;8(5):e62685.[148]	series (multi-centre) Period: October 2011–May 2012 Location: South Korea	laboratory-confirmed influenza virus infection Presentation: Sudden onset of fever (≥37.8°C) and presence of at least one of the following respiratory symptoms: cough, sore throat, or rhinorrhea/nasal obstruction Viral testing: RIDT (performed bedside) and RT-PCR	B (2011–2012) n=656 of 850 (77.2%) ED cases infected with influenza A(H3N2) and 194 (22.8%) with influenza B n=68 of 79 (86.1%) hospitalized cases infected with influenza A(H3N2) and 11 (13.9%) with influenza B	Age group: Adults Age at hospitalization: n=79 of 79 (100.0%) hospitalized cases ≥18 years of age	cases had cerebrovascular disorders and 5 (0.6%) had neuromuscular diseases (n=279 [32.8%] ED cases had at least one comorbid condition). **Hospitalization** n=9 of 79 (11.4%) hospitalized cases had cerebrovascular disorders and 3 (3.8%) had neuromuscular diseases (n=54 [68.4%] hospitalized cases had at least one comorbid condition). Neuromuscular disease was a significant predictor of hospitalization in ED presentations with laboratory-confirmed influenza virus infection (aOR: 10.18, 95% CI: 1.30–79.40, p=0.027). Cerebrovascular disorder was significantly associated with hospitalization in ED presentations with laboratory-confirmed influenza virus infection in univariate analysis (OR: 4.18, 95% CI: 1.86–9.39, p<0.001), but not in multivariate analysis (aOR: 1.42, 95% CI: 0.52–3.85, p=0.490).	n/a
Wieching A, Benser J, Kohlhauser-Vollmuth C, Weissbrich B,	Design: Population case series	Case definition: Patient (<18 years of age) hospitalized with	Pandemic influenza A(H1N1)pdm09	n=94 hospitalized cases (n=6 [6.4%] ICU cases)	**Hospitalization** n=8 of 94 (8.5%) hospitalized cases had neurologic	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
Streng A, Liese JG. Clinical characteristics of pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Northern Bavaria, Germany. BMC Res Notes. 2012;5:304.(149)	Period: July 2009–March 2010 Location: Germany (Northern Bavaria)	laboratory-confirmed influenza virus infection Viral testing: RT-PCR or DFA test, with DFA-positive tests subtyped by RT-PCR		Age group: Children Median age at hospitalization: 7 years (IQR: 3–12 years) Age range at ICU admission: 0.1–16 years	disorders (n=40 [42.6%] hospitalized cases had at least one underlying medical condition). **ICU admission** n=2 of 6 (33.3%) ICU cases had neurologic disorders (n=4 [66.7%] ICU cases had at least one underlying medical condition).	
Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004-2012. Pediatrics. 2013;132(5):796-804.(150) *(Dataset overlaps with Blanton L, et al. Pediatrics. 2012;130(3):390-6.(22) and Cox CM, et al. Clin Infect Dis. 2011;52 Suppl 1:S69-74.(39) [Pandemic deaths])*	Design: Population case series Period: October 2004–September 2012 Location: USA	Case definition: Death associated with laboratory-confirmed influenza virus infection in patients <18 years of age Viral testing: RIDT, viral culture, fluorescent antibody, enzyme immunoassay, RT-PCR, or immunohistochemical staining of tissue Risk group definition: ACIP	Seasonal influenza A and B and pandemic influenza A(H1N1)pdm09 (2004–2005 through 2011–2012, including pandemic influenza season) n=649 of 830 (78.2%) fatal cases infected with influenza A, 165 (19.9%) with influenza B, 1 (0.1%) with influenza A and B, and 15 (1.8%) with type undetermined	n=830 fatal cases (n=794 [95.7%] fatal cases with available information on underlying health status) Age group: Children Median age at death: 7 years (IQR: 1–12 years)	**Death** n=260 of 794 (32.7%) fatal cases had a neurologic disorder, including neurodevelopmental disorder (n=212; cerebral palsy, n=78), neuromuscular disorder (n=25), and seizure disorder (n=126) (n=453 [57.1%] fatal cases had at least one ACIP-defined high-risk medical condition).	Level III n/a
Zheng Y, He Y, Deng J, et al. Hospitalized children with 2009 influenza a (H1N1) infection in Shenzhen, China, November-	Design: Clinical case series (single centre) Period:	Case definition: Patient (children; age range not defined) hospitalized with influenza-like symptoms and laboratory-confirmed	Pandemic influenza A(H1N1)pdm09	n=148 hospitalized cases Age group: Children Age range at hospitalization: 0.2–13.9 years	**Hospitalization** n=1 of 148 (0.7%) hospitalized cases had cerebral palsy and developmental delay (n=22 [14.9%] hospitalized cases	Level III n/a

Study	Study design	Study population and method of influenza virus testing	Influenza type/subtype/ vaccine (season)	Participants*	Summary of key findings**	Level and quality of evidence***
December 2009. Pediatr Pulmonol. 2011;46(3):246-52.(151)	November–December 2009 Location: China	influenza virus infection Presentation: Influenza-like symptoms: fever and cough or sore throat Viral testing: rtRT-PCR			had underlying chronic disease).	
Zinman L, Thoma J, Kwong JC, Kopp A, Stukel TA, Juurlink DN. Safety of influenza vaccination in patients with myasthenia gravis: a population-based study. Muscle Nerve. 2009;40(6):947-51.(152)	Design: Population self-controlled case series Period: 1992–2007 Location: Canada (Ontario)	Case definition: Patient (≥18 years of age) with a history of MG and subsequent hospital admission for MG within 42 weeks of influenza vaccination Influenza vaccination status: Registry record	Seasonal influenza vaccine	n=513 patients hospitalized for MG within 42 weeks of influenza vaccination Age group: Adults Median age of MG patients: 74.0 years (IQR: 64.5–79.5 years)	**Post-vaccination (exacerbation)** Vaccination of MG patients against influenza was not associated with exacerbation of MG; no increased risk of hospitalization for exacerbation of MG following influenza vaccination during the risk interval (0–6 weeks post-vaccination) compared to the control interval (18–42 weeks post-vaccination) (relative incidence: 0.84, 95% CI: 0.65–1.09).	Level III n/a

Abbreviations: Refer to section V. List of Abbreviations.

* Pediatric and adult age ranges were defined according to the age group delineations used in the Statement (i.e., <18 years of age for children and ≥18 years of age for adults).

** Reported frequencies of specific NNCs may sum to greater than the total number of study subjects with NNCs, as subjects may have more than one NNC. Subgroup analyses with fewer than five total cases (e.g., deaths among hospitalized cases) were not extracted. Terminology for NNCs and specific NNCs was extracted as reported from studies; therefore, the terminology for the same NNC may not be consistent across studies included for review or with that used in the present literature review (e.g., neurologic condition vs. neurological disease).

*** Methodological quality of studies was rated for designs outlined by the Harris et al. (2001) design-specific criteria for grading the internal validity of individual studies(7).