

Institute of Medicine

**Committee on Implementation of Antiviral Medication
Strategies for an Influenza Pandemic**

Diagnosis of Influenza in Children

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DEDICATED TO THE HEALTH OF ALL CHILDREN™



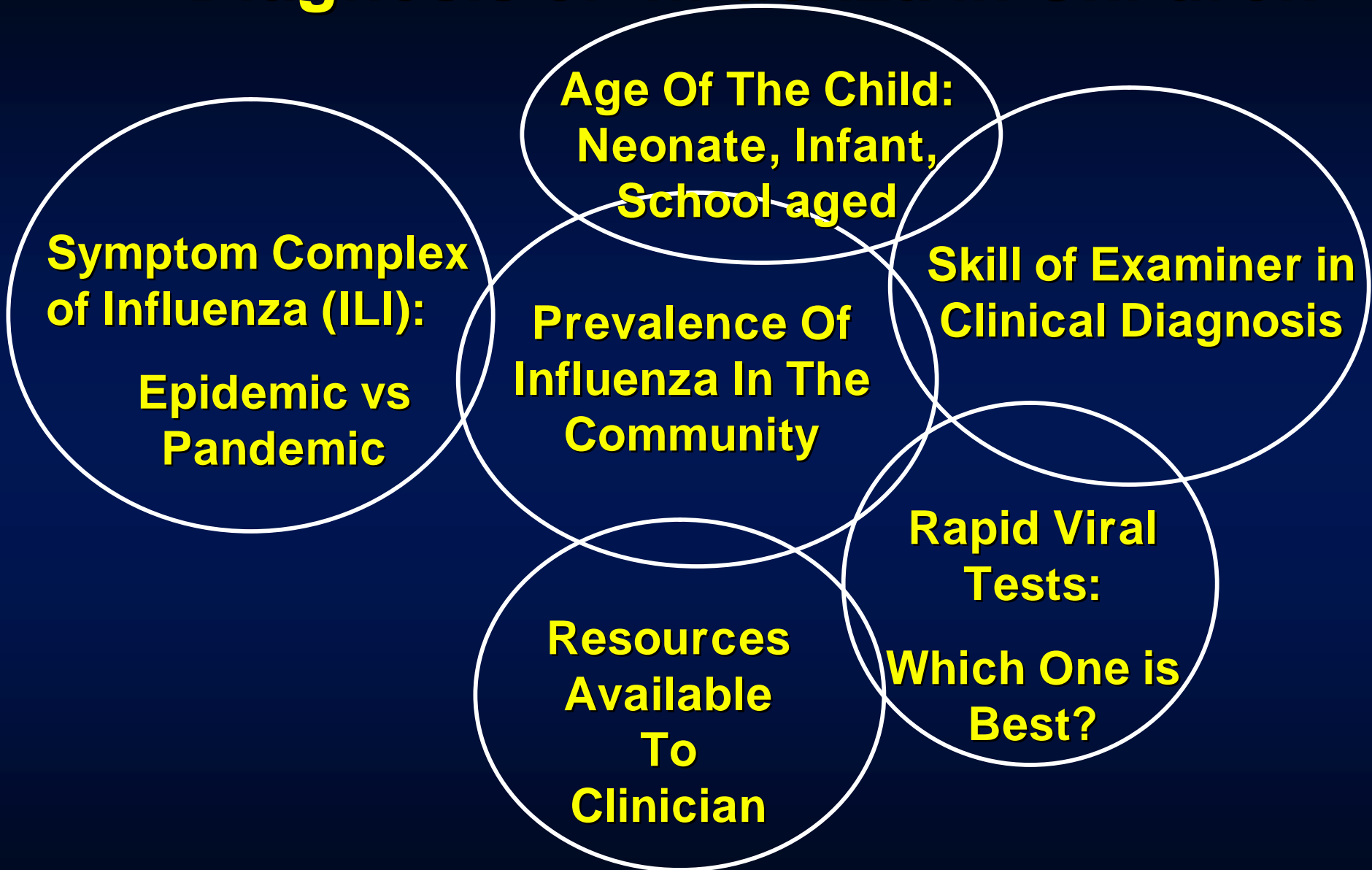
Diagnosis of Influenza in Children

- How is influenza currently diagnosed in children by primary care practitioners?
- How will pandemic influenza differ from epidemic influenza?

Diagnosis of Influenza in Children

1. Access to medical care for children
2. Clinical diagnosis of influenza in children
3. Laboratory diagnosis of diagnosis of influenza in children

Diagnosis of Influenza in Children



Diagnosis of Influenza in Children

Variables: Symptoms of Influenza

- **Studies differ in definitions**
 - **Any fever**
 - **Higher sensitivity, lower specificity**
 - **Fever to 40 C, coryza, cough, headache**
 - **Lower sensitivity, but higher specificity**

Diagnosis of Influenza in Children

Variables: Symptoms of Influenza

- **Children acquire many seasonal lower respiratory tract viral infections that mimic epidemic influenza symptoms:**
 - **RSV**
 - **Metapneumovirus**
 - **Parainfluenza**
 - **Adenovirus**
 - **Rhinovirus**
 - **etc**

Diagnosis of Influenza in Children

Variables: Skill of Examiner

- **Pediatrician**
 - NP
 - PA
- **Emergency Medicine staff in the ED**
- **Family Practice staff**

Diagnosis of Influenza in Children

Variables: Prevalence in Community

- **We wish to diagnose EARLY in a Pandemic for epidemiology, when the sensitivity and specificity of both clinical and laboratory diagnosis are least accurate**
- **We also wish to diagnose DURING the Pandemic for treatment, when positive and negative predictive values are most accurate**

Diagnosis of Influenza in Children

Variables: Resources Available


- **Resources in medical offices are highly variable: hiring competent personnel (from MD's to MA's), laboratory support, availability of POC test kits in clinic, hospital/ED support for additional studies**
 - **Scripps Clinic**
 - **HMO (Kaiser system in California)**
 - **Children's Hospital (ED, Clinics)**
 - **SD County Community Clinics**

Diagnosis of Influenza in Children

Variables: Rapid Viral Tests

- **Which test is best for children?**
 - Directogen? Biostar? Quickvue? Etc?
- **Which sample is obtained?**
 - Nasopharyngeal swab, nasal wash, throat swab
- **Who gets the sample and how competent are they?**
- **Which lab runs the test for your patient?**
 - Clinic personnel: results impact management
 - Hospital or reference lab: not timely

How the Child Gets to the Practitioner

- Child develops symptoms of influenza
 - Parent (school/daycare) assesses need for medical care
 - How accurate is the parent/school/daycare?
 - Parent takes child to clinic for Dx, Rx
 - Other points of diagnosis, less centralized, during a pandemic?
 - Clinician diagnoses influenza (clinical/lab)
 - Treatment initiated, if appropriate
 - Pandemic antiviral distribution mechanisms?
- 

Need to Decrease Exposures of Children to Pandemic Flu

- **Traditionally, the most cost-efficient and best care: bring all children to a central clinic (the medical home) for Dx and Rx**
 - **One way to spread influenza is a crowded waiting room (most clinics do not have “sick” waiting rooms; all sick children in the “sick” waiting room won’t have influenza)**
- **De-centralize point-of-care testing: schools, daycare centers, pharmacies, households (for the pandemic).**

Diagnosis of Influenza in Children

How Good Are We at Diagnosis?

- **Of Children with “ILI,” what percent actually have Influenza?**
- **Of Children diagnosed with Influenza, what is the spectrum of symptoms?**

How Good Are We at Diagnosis?

“High” Sensitivity ILI Screening

- **Whitley 2001 (oseltamivir trial):**
 - When surveillance indicated epidemic was present:
 - Children 1-12 years, with less than 48 hours of illness, were screened for:
 - Oral/otic temp ≥ 37.8 C
 - One respiratory symptom (cough, coryza)
 - RSV-negative by rapid testing
 - Multiple symptoms recorded and tracked

Whitley RJ et al. PIDJ 2001;20:127-33

How Good Are We at Diagnosis?

“Higher” Sensitivity ILI Screening

- Hedrick 2000 (zanamivir trial):
 - When surveillance indicated epidemic was present:
 - Children 5-12 years, with less than 36 hours of influenza-like-illness (not further defined), were screened for:
 - Temp ≥ 37.8 C (only)
 - Multiple symptoms recorded and tracked

Hedrick JA et al. PIDJ 2000;19:410-17.

How Good Are We at Diagnosis?

Table 4. Summary of positive predictive values (PPV) for fever, cough, and fever plus cough across studies, as well as single and combination signs/symptoms shown to be important in analysis-specific logistic models, from trials of the influenza antiviral agents zanamivir and oseltamivir, in children <13 years.

PPV for single and for combined sx:

Single or combined signs/symptoms

	Zanamivir trial, children aged 5–12 years (n = 268)	Oseltamivir trial, children aged 5–12 years (n = 255)	Oseltamivir trial, children aged 1–4 years (n = 221)
Fever ^a	79 (75–83)	69 (63–75)	65 (58–71)
Cough	77 (73–81)	70 (64–75)	64 (58–71)
Fever + cough	83 (79–88)	71 (65–77)	64 (58–71)
Fever + cough + WBC count <4500/mm ³	94 (89–99)
Cough + headache	...	73 (67–80)	...
Fever + cough + headache	...	74 (68–81)	...
Myalgia	73 (66–81)
Fever + cough + myalgia	72 (64–81)

NOTE. Data are PPV, % (95% CI). PPV was calculated as the probability of having laboratory-confirmed influenza virus infection when a symptom alone or in combination was present.

^a Measured body temperature $\geq 38.2^{\circ}\text{C}$.

Ohmit SE and Monto AS. CID 2006;43:564-8.

Clinical Prediction Rule

ED setting
pediatric Hospital, 2002-3
Age 6.2 yrs (\pm 5.2 yrs)

Friedman MJ 2004

Table 2. Univariate Analysis of Clinical Features of Influenza-Positive Patients

Finding	Frequency of Reported Symptom, %	OR (95% CI)
Historical		
Fever, $\geq 39^{\circ}\text{C}$	55	2.4 (1.2-5.0)
Rhinorrhea	60	0.8 (0.4-1.7)
Cough	83	2.2 (1.0-5.2)
Vomiting	36	1.6 (0.7-3.4)
Diarrhea	10	0.8 (0.3-2.2)
Decreased intake	57	1.0 (0.5-2.0)
Decreased activity	54	1.8 (0.8-3.6)
Headache*	44	2.6 (1.2-5.8)
Abdominal pain and/or nausea*	31	3.2 (1.2-8.2)
Sore throat	37	1.5 (0.7-3.2)
Myalgia*	33	0.8 (0.4-1.8)
Apnea†	0	0.5 (0.0-3.9)
Clinical		
Coryza	57	1.6 (0.8-3.2)
Cough (observed)	33	1.3 (0.6-2.9)
Wheezing	5	0.3 (0.1-1.0)
Rales	3	0.5 (0.1-2.4)
Retractions	0	0.1 (0.0-0.6)
Nasal flaring	0	0.2 (0.0-1.2)
Rash	10	1.6 (0.3-8.1)
Conjunctivitis	3	0.6 (0.1-3.7)
Pharyngitis	35	2.0 (0.9-4.3)
Cervical adenopathy	14	1.7 (0.6-5.4)
Otitis media	10	1.0 (0.3-3.3)
Abdominal tenderness	12	1.8 (0.5-6.0)

Diagnosis of Influenza in Children

Clinical Prediction Rule

- The triad of cough and headache by history and clinical finding of pharyngitis
- Sensitivity: 80% (95% CI, 69%-91%)
- Specificity of 78% (95% CI, 67%-89%)
- PPV of 77% (95% CI, 61%-88%)
- NPV of 81% (95% CI, 70%-92%)

Table 2. Characteristics of Hospitalizations Attributable to Influenza, According to Age Group (2000–2004).

Characteristic	Age of Patient			P Value
	0–5 Mo (N= 79)	6–23 Mo (N= 49)	24–59 Mo (N=32)	
Length of stay — days				0.40
Median	2	2	2	
Range	1–7	0–15	1–17	
Admission to ICU — no. (%) [*]	2 (3)	2 (4)	3 (9)	0.22
Antibiotic requirement — no. (%)	10 (13)	15 (31)	11 (34)	0.01
Bacterial coinfection — no. (%)	1 (1)	0	0	1.00
Viral coinfection — no. (%)	12 (15)	7 (14)	3 (9)	0.72
Diagnostic evaluation — no. (%)				
Chest radiograph	36 (46)	37 (76)	23 (72)	0.001
Blood culture	59 (75)	30 (61)	16 (50)	0.03
Urine culture	56 (71)	11 (22)	7 (22)	<0.001
Cerebrospinal fluid culture	48 (61)	6 (12)	0	<0.001
Discharge diagnosis — no. (%)				
Influenza	22 (28)	12 (24)	11 (34)	0.62
Bronchiolitis	20 (25)	10 (20)	1 (3)	0.02
Pneumonia	4 (5)	9 (18)	5 (16)	0.04
Asthma	1 (1)	6 (12)	2 (6)	0.02
Seizure	0	4 (8)	3 (9)	0.01
Viral illness	17 (22)	3 (6)	9 (28)	0.02
Fever/suspected sepsis	15 (19)	5 (10)	1 (3)	0.06

**Influenza
Hospitalization
in Children
New Vaccine
Surveillance
Network**

**Poehling
NEJM 2006**

How Good Are We at Diagnosis? New Vaccine Surveillance Network

- Of children admitted to a hospital with proven influenza, only 24 to 34% had a discharge diagnosis of influenza
 - Pediatricians don't know influenza when they see it?
 - Pediatricians are inaccurate at coding?

Poehling KA et al. NEJM 2006;355:31-40.

Diagnosis of Influenza in Children

Rapid Tests

- **Point-of-Contact test for pandemic diagnosis/epidemiology, early treatment**
 - Many technologies currently available
 - New technologies being developed (PCR, gene chip array)
 - Sampling techniques vary: np swab, nasal wash, throat swab (mucus in a tissue?)
 - Comparisons usually between rapid test and culture (or PCR)

Rapid Tests

Uyeki T PIDJ 2003

TABLE 4. Rapid influenza diagnostic test studies among children

Author, Year	Test	Population	Specimen Type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Comparison
Rodriguez et al., ⁵⁶ 2002	Directigen Flu A	Primarily children	NS	95	84	86	94	Viral culture
	ZostatFlu		TS, NW	72	83	80	78	
	FLU OIA	Some adults	NS	93	82	84	92	
	QuickVue	(<i>N</i> = 118)	NS	95	75	81	95	
Noyola et al., ⁵⁵ 2000	ZostatFlu	Primarily children (mean age, 3.8 yr; range, 0–27 yr) (<i>N</i> = 479)	NW, NA	70.1	92.4	76.3	89.9	Viral culture
Noyola et al., ⁵⁵ 2000	ZostatFlu	Children (median age, 2.8 yr) (<i>N</i> = 198)	TS, NW	96	77	89	98	Viral culture
Mitsumura et al., ⁵⁷ 2000	ZostatFlu	Children (<i>N</i> = 176)	TS (<i>N</i> = 102)	87.4	62.7	43.1	72.8	Viral culture
			NA (<i>N</i> = 74)	48.1	90.0	92.9	59.1	
Hulsen et al., ⁵⁸ 2001	ZostatFlu	Children, adults (<i>N</i> = 398)	TS	85	83	79	70	Viral culture
Dominguez et al., ⁴⁸ 1995	Directigen Flu A	Children (<i>N</i> = 81)	NW, TS	75	100	NR	NR	Viral culture
Noyola et al., ⁵⁵ 2000	Directigen Flu A	Primarily children (mean age, 3.8 yr; range, 0–27 yr) (<i>N</i> = 417)	NW	89.7	98.1	95.5	96.9	Viral culture
Waner et al., ⁵⁹ 1991	Directigen Flu A	Children (<i>N</i> = 190)	NPW, TS, TA, SP, RW, PG	100	91.0	82.8	100	Viral culture
Shimiz, ⁶⁰ 1998	Directigen Flu A	Children	TS (<i>N</i> = 48)	77.9	98.4	NR	NR	Viral culture
			NPA (<i>N</i> = 176)	92.1	100	NR	NR	
Mitsumura et al., ⁶¹ 1998	Directigen Flu A	Children (mean age, 3.7 yr) (<i>N</i> = 116)	NR	90	90	NR	NR	Viral culture, serology
Boon et al., ⁶² 2001	Directigen Flu A	Children 12–19 yr (<i>N</i> = 37)	NPS	85	84.6	NR	NR	Viral culture
Ryan-Poirier et al., ⁶⁴ 1992	Directigen Flu A	Children, adults (<i>N</i> = 41)	PG	39	NR	NR	NR	Viral culture
			NPW	90	NR	NR	NR	
Marcante et al., ⁶³ 1998	Directigen Flu A	Children, adults (<i>N</i> = 41)	NPA	64.2	NR	NR	NR	Shell vial cult
Reina et al., ⁶⁵ 1998	Directigen Flu A	Children with lower respiratory tract symptoms, negative for other viruses (<i>N</i> = 377)	NPA	84.7	100	100	97.2	Shell vial cult
Hamilton et al., ⁶⁶ 2002	Directigen Flu A + B	Children ≤19 yr (median age, 20 mo) (<i>N</i> = 300)	NA	75	95	74	95	Viral culture
Reina et al., ⁶⁷ 2002	Directigen Flu A + B	Children (<i>N</i> = 95)	NPA	93.6 (A)	100	100	92.1	Shell vial cult
				82.8 (B)	100	100	88.8	
Yamazaki et al., ⁶⁸ 2000	Directigen Flu A + B	Children (<i>N</i> = 259)	NPA	89.8 (A)	95.8 (A)	96.8 (A)	89.1 (A)	Viral culture
				88.9 (B)	88.1 (B)	76.2 (B)	94.9 (B)	
Chan et al., ⁶⁹ 2002	Directigen Flu A + B	Primarily children Some adults (<i>N</i> = 250)	NPA	100 (A)	98.7 (A)	88 (A)	100 (A)	Viral culture
				87.6 (B)	92.8 (B)	80 (B)	98.1 (B)	
Schukro et al., ⁷⁰ 2001	FLU OIA	Children ≤18 yr (<i>N</i> = 270)	NA, NPS, TS, SP	71.8	98.7	NR	NR	Viral culture
Mitsumura et al., ⁷¹ 1999	FLU OIA	Children (<i>N</i> = 103)	NPA (<i>N</i> = 42)	80	68.8	NR	NR	Viral culture
			TS (<i>N</i> = 61)	36.7	83.9			
Yamazaki et al., ⁷² 1999	FLU OIA	Children (<i>N</i> = 92)	NA	88.6	68.2	NR	NR	Viral culture

Diagnosis of Influenza in Children

Rapid Tests (Uyeki 2003)

Test	Sens	Spec	PPV	NPV
DFA	57-80	92-100	72-85	89-99
Directogen	64-95	85-100	62-100	94-100
Flu OIA	72-88	65-96		
QuickVue	76-93	89-94	49-94	86-91
NOW Flu A	58	99	94	89

Rapid test	Influenza A			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Binax Now Influenza A&B	36/49 (73)	127/128 (99)	36/37 (97)	127/140 (91)
3M Directigen EZ Flu A + B	34/49 (69)	128/128 (100)	34/34 (100)	128/143 (89)
Denka Seiken Quick Ex-Flu	35/49 (71)	128/128 (100)	35/35 (100)	128/142 (88)
Abbott Espline Influenza A&B-N	33/49 (67)	128/128 (100)	33/33 (100)	128/144 (88)
Rockeby Influenza A Antigen Test	5/49 (10)	128/128 (100)	5/5 (100)	128/172 (72)
3M QuickVue Influenza A +B Test	33/49 (67)	128/128 (100)	33/33 (100)	128/144 (88)

6 Rapid Flu A Tests in Children Melbourne, Australia

Smit M et al. *Diag Micro Infect Dis* 2007;57:67-70

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Sensitivity of rapid test kits based on data selected from different patient age ranges

Rapid test	Influenza A sensitivity (%); age range			
	0-2 years	0-5 years	0-15 years	All ages
Binax Now Influenza A&B	23/27 (89)	30/33 (91)	34/40 (85)	36/49 (73)
3M Directigen EZ Flu A + B	23/27 (89)	29/33 (88)	32/40 (80)	34/49 (69)
Denka Seiken Quick Ex-Flu	23/27 (89)	29/33 (88)	33/40 (83)	35/49 (71)
Abbott Espline Influenza A&B-N	22/27 (85)	28/33 (85)	31/40 (78)	33/49 (67)
Rockeby Influenza A Antigen Test	4/27 (15)	4/33 (12)	5/40 (13)	5/49 (10)
3M QuickVue Influenza A +B Test	23/27 (89)	28/33 (85)	31/40 (78)	33/49 (67)

Rapid Pediatric Tests for the Pandemic Gene Array vs PCR vs Immunoassay

TABLE 1. Assay performance summary and comparison

Assay	% Indicated value (95% confidence interval)			
	Sensitivity	Specificity	PPV	NPV
Referenced to viral culture				
MChip	98 (91–100)	98 (89–100)	98 (91–100)	98 (88–100)
QuickVue	93 (83–97)	100 (92–100)	100 (93–100)	92 (81–97)
RT-PCR	98 (90–100)	89 (77–95)	92 (82–96)	98 (87–100)
Referenced to RT-PCR				
MChip	92 (82–96)	98 (87–100)	98 (91–100)	89 (77–95)
QuickVue	85 (74–92)	97 (87–100)	98 (90–100)	82 (69–90)
Viral culture	92 (82–96)	98 (87–100)	98 (91–100)	89 (77–95)

Mehlmann M et al. J Clin Micro 2007;455:1234-37.

Diagnosis of Influenza in Children

Summary

- **Clinical diagnosis of influenza is about 60-70% sensitivity, with PPV about 70-80% across all pediatric age groups; lowest in young infants**
- **Rapid viral tests (current) demonstrate about 70-80% sensitivity, with PPV about 80-90% across all tests and sample acquisition techniques**
- **In a pandemic, social distancing would support decentralized POC lab dx in locations other than the doctor's office**

Diagnosis of Influenza in Children

- **Thank you for your efforts on behalf of children!**