ADVANCES IN RESPIRATORY VIRUS DIAGNOSTICS: MOLECULAR AND POC TESTING

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Outline

1. Viral respiratory infections
    1. Rationale / importance of diagnostic testing
    2. Test methods
    3. Accuracy of rapid tests for RSV and influenza
    4. Impact of diagnostic testing on antimicrobial prescribing

Acute Respiratory Infection (ARI)

- Most common acute illness regardless of age or gender[1]
- Severe disease leading to hospitalization:
  - Bronchiolitis (infants)
  - Pneumonia
  - Exacerbations of underlying chronic disease in high-risk adults and elderly
    - COPD
    - Asthma
    - Cardiac
- Second leading cause of death in children <5 years old across all regions of the world[2]
- Most ARI are caused by viruses, especially in children[1]

[1]Monto AS. Epidemiology of viral respiratory infections. *Am J Med* 2002.

[2]Mathers CD, *et al*. The burden of disease and mortality by condition: data, methods, and results for 2001. Oxford University Press 2006.

Most ARI are caused by viruses – especially in children

Prospective study of children < 3 years old with ARI, Quebec City, 2006-10

	Total N=1039 n (%)	Hospitalised N=734 n (%)	Clinic N=305 n (%)
≥ 1 virus	**908 (87.4)**	**632 (86.1)**	**276 (90.1)**
1 virus	752 (72.4)	546 (74.4)	206 (67.5)
2 viruses	144 (13.9)	85 (11.6)	59 (19.3)
3 viruses	11 (1.1)	1 (0.1)	10 (3.3)
4 viruses	1 (0.1)	0	1 (0.3)

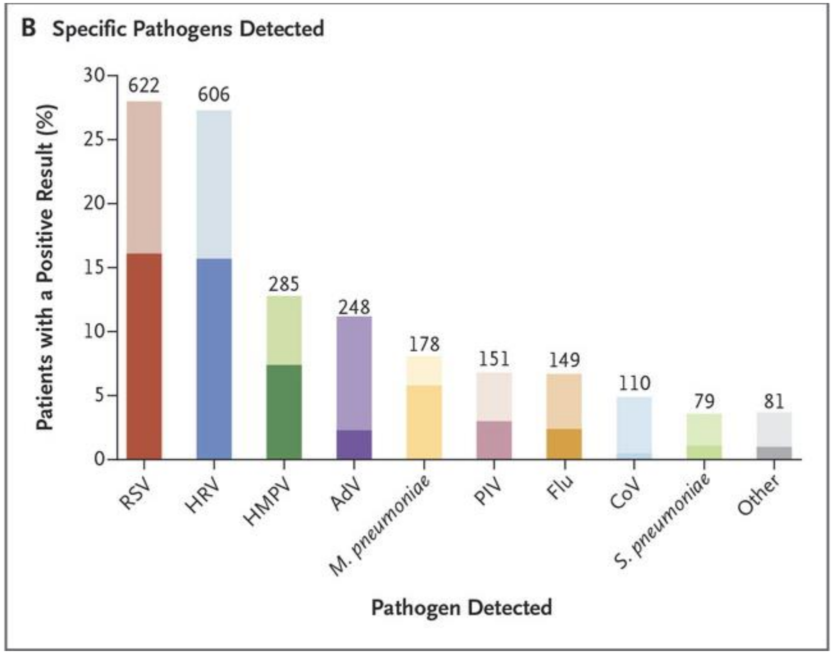
Papenburg et al. Comparison of risk factors for human metapneumovirus and RSV disease severity in young children. *J Infect Dis* 2012.

RSV disease burden in children

- **Most common cause of lower respiratory tract infections among young children worldwide[1, 2]**
  - "Estimated that globally in 2015, 33.1 million episodes of RSV-ALRI, resulted in about 3.2 million hospital admissions, and 59 600 in-hospital deaths in children younger than 5 years."[3]

1- Hall et al. *N Engl J Med* 2009
2- Nair et al. *Lancet* 2010
3- Shi et al. Lancet 2017

Pathogens Detected in U.S. Children with Community-Acquired Pneumonia Requiring Hospitalization



Jain et al., *N Engl J Med* 2015

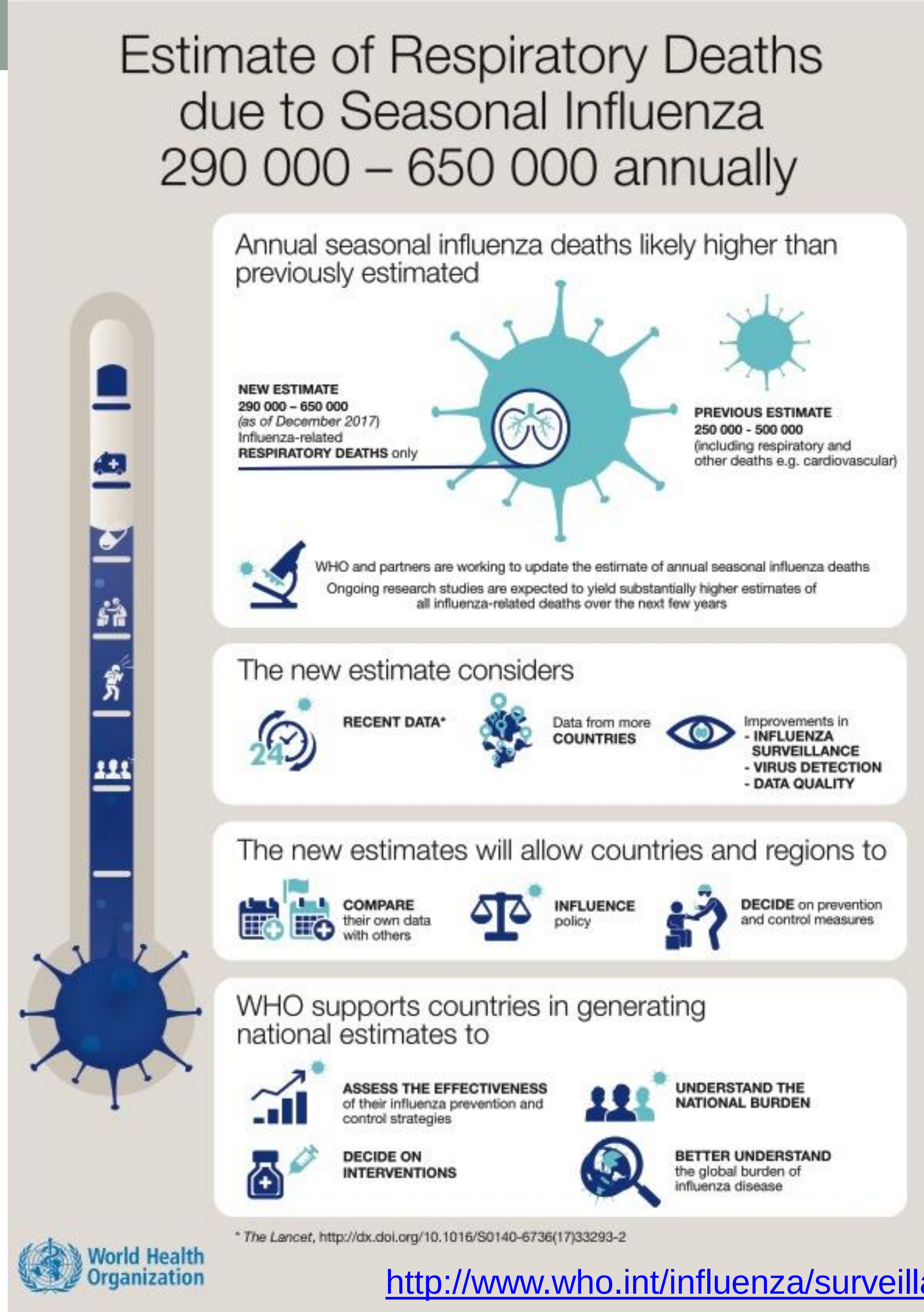
Underrecognized burden of RSV in adults

- Among adults, RSV infection accounts for approximately:
  - 11% of hospitalizations for pneumonia[1]
  - 11% of hospitalizations for COPD[1]
  - 7% of hospitalizations for asthma[1]
  - 5% of hospitalizations for congestive heart failure[1]
  - 18% of office visits by elderly for respiratory illnesses during winter[2]

- *Even during peak influenza periods*, RSV causes
  - 6% of ARI hospitalizations among elderly >75 years old in Québec[3]

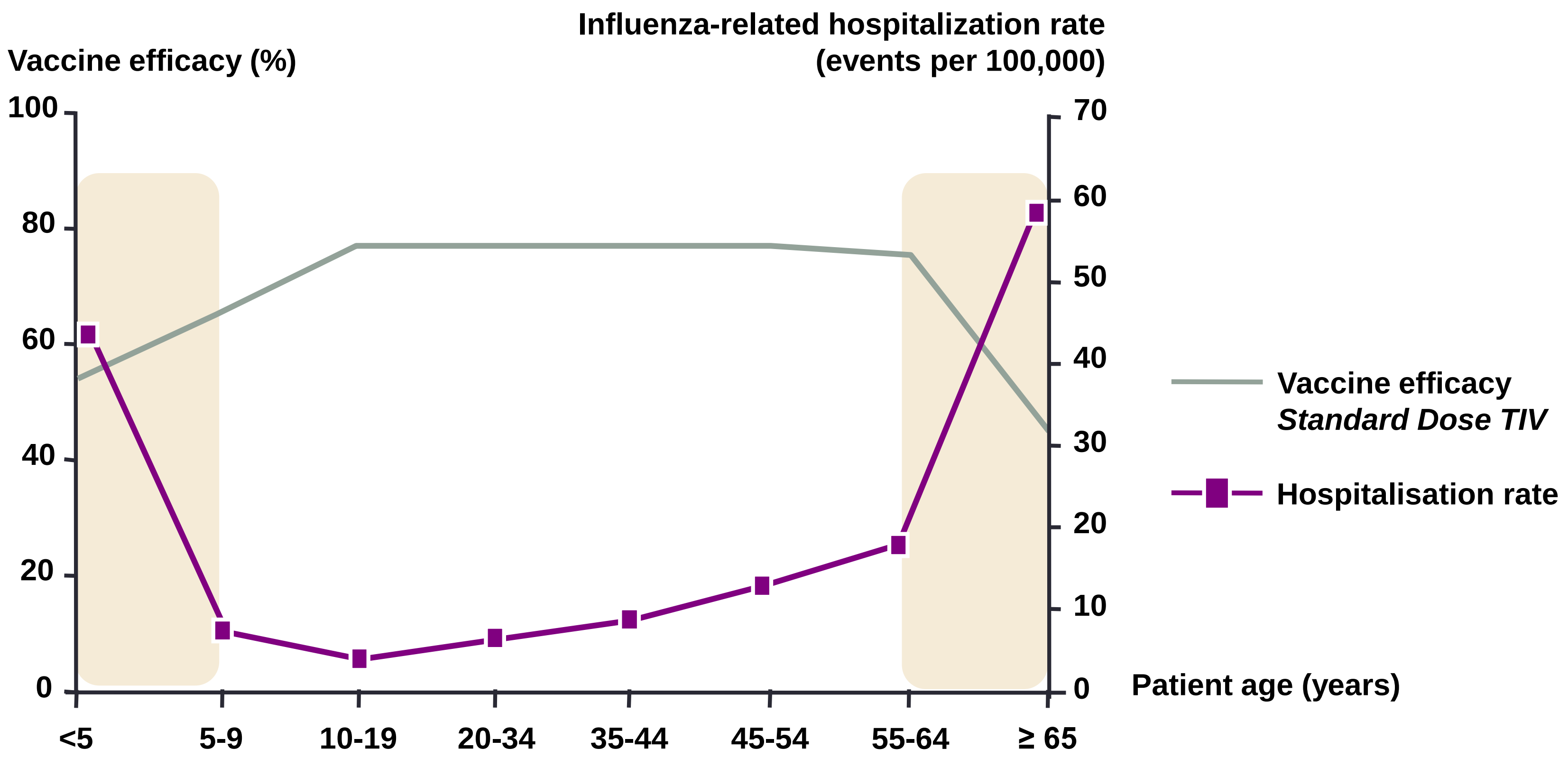
- This leads to, yearly, in U.S. population > 65 years old:
  - ➢ 177,000 hospitalizations[1,3]
    - Hospitalization costs alone would exceed $1 billion[1,4]
  - ➢ 10,000 - 14,000 deaths[1,3]

1. Falsey et al. N Engl J Med 2005; 2. Thompson et al. JAMA 2003;
3. Gilca et al Open Forum Infect Dis 2014; 4. Zambon et al. Lancet 2001; 5. Han et al. J Infect Dis. 1999



http://www.who.int/influenza/surveillance_monitoring/bod/en/

Extremes of Age: Influenza Vaccine Efficacy Lowest, Related Complications Highest



[1] *Nichol K, et al. Vaccine 2003; 21:1769-1775*
[2] *Goodwin K, et al. Vaccine 2006; 24:1159-1169*
[3] *Grubeck-Loebenstein B, et al. Nat Med 1998; 4:870*
[4] *Glezen WP, et al. Am Rev Respir Dis 1987; 136:550-555*

High-risk Groups

People at high risk of influenza-related complications or hospitalization	
• **Adults aged >60 years; residents of nursing homes or long-term care facilities**	• Renal disease; liver disease
• **All children aged <5 years, especially 6 to 23 months**	• Children receiving chronic ASA
• Chronic cardiac disorders	• Endocrine/metabolic disorders (diabetes)
• Chronic pulmonary disorders and asthma	• Anemia, hemoglobinopathy
• Cancer/immune-compromising conditions, including HIV/AIDS patients	• Conditions compromising the evacuation of respiratory secretions
• Extreme obesity	• Healthy pregnant women (T2/T3)
• People in isolated/distant communities;	• High-risk pregnant women at any stage

ASA = aspirin; T2/T3 = trimester 2/3

Government of Canada. https://www.canada.ca/en/public-health/services/diseases/flu-influenza/health-professionals-flu-influenza.html

Clinical characteristics cannot distinguish RSV and influenza from other respiratory pathogens

- Clinical influenza-like illness case definitions lack sensitivity and specificity
- Pneumonia on chest x-ray in 20-50% of hospitalized patients
  - Viral? Bacterial? Both?

Laboratory diagnosis required for confirmation of etiology

Table 1 Clinical manifestations of respiratory syncytial virus infection compared with symptomatic influenza A disease [20, 21, 27, 36]

Symptoms	RSV (%)	Influenza (%)
Cough	85–95	89
Dyspnea	51–93	32
Wheezing	33–90	30
Rhinorrhea	22–78	64
Sore throat	16–64	64
Myalgias	10–64	70
Fever	48–56	72

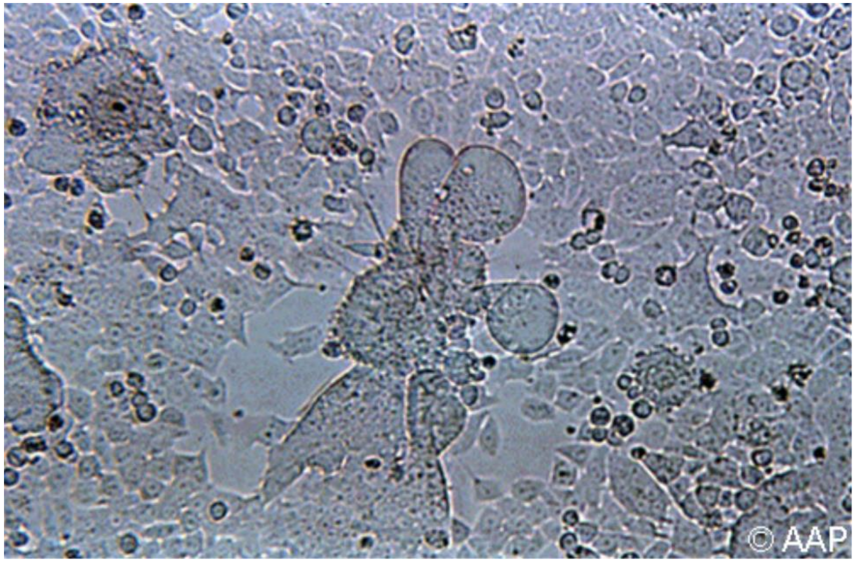
RSV respiratory syncytial virus

Branche AR, Falsey AR. *Drugs Aging.* 2015;32(4):261-9.

TRADITIONAL RESPIRATORY VIRUS DIAGNOSTICS

Cell culture

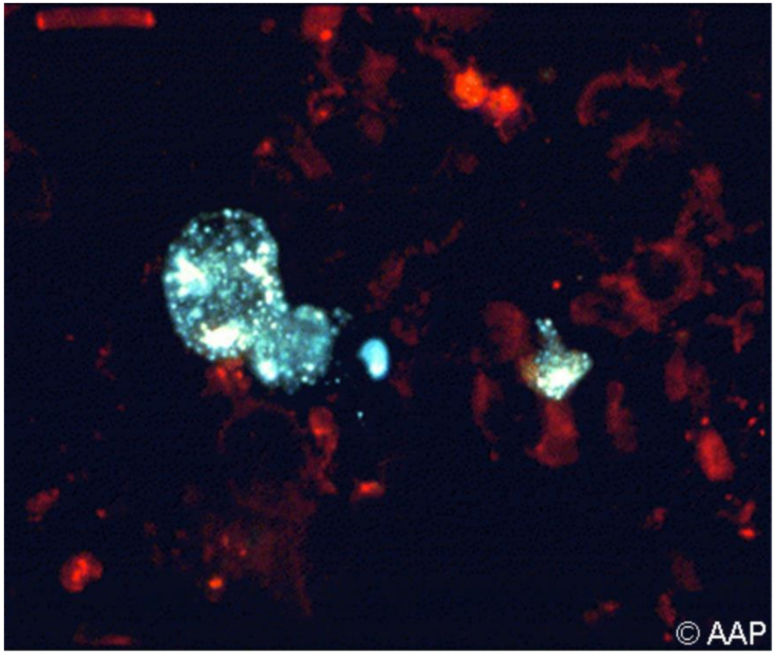
- Lacks sensitivity
  - ~50-70%
- Slow
  - 24-48h to several days
- Labour-intensive
- Laboratory expertise
- Useful for phenotypic testing
  - Antigenic characterization
  - Antiviral resistance



Characteristic cytopathic effect of RSV in tissue culture: formation of large multinucleated syncytial cells.

Immunofluorescent staining

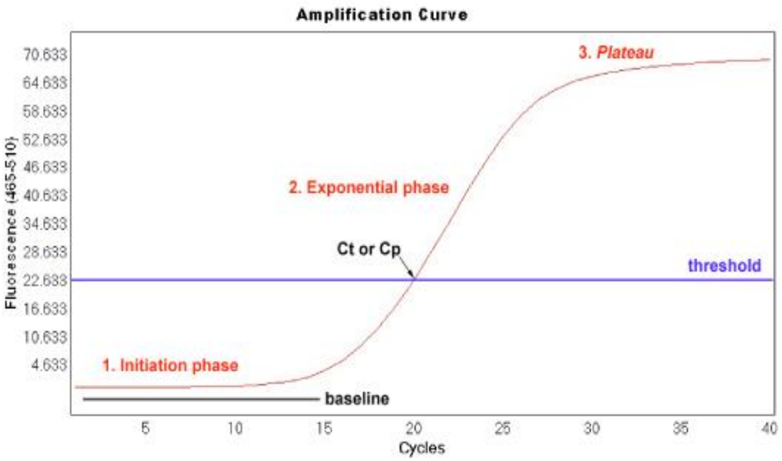
- Multiplex panels available for
  - RSV
  - Influenza A & B
  - hMPV
  - PIV 1-4
  - Adenovirus
- Sensitivity of 50-90%
- Tech. time 1-2h
- Technical expertise



RSV antigen in nasopharyngeal secretions: green immunofluorescence

Laboratory-based molecular assays: RT-PCR

- Gold standard methods
  - Low limits of detection: ➔ high clinical sensitivity
- Commercial or lab-developed
  - Not all perform equally well
- Can be highly multiplexed:
  - 12-18 targets
  - Bacterial targets
- Most assays complex, require batching
  - Result turnaround time >>> analytical time
- Greater automation
  - Higher thotughput



Huggett J and O'Grady J. 2014.

MUHC 24/7 lab serves ~1.8 million people

~10,000 respiratory virus tests per year:

- Lab-developed (in 2008-09) real-time PCR assay
- Mean TAT 8-12 hours (for Glen site)
- 12 targets:
  - RSV, Influenza A/B, Parainfluenza 1/2/3, Adenovirus, Coronavirus 229E/OC43, Human Metapneumovirus, Enterovirus, and Rhinovirus

Laboratory:
High volume / highly multiplexed

Analytes

Panel 1 (CE-IVD Marked)	Panel 2 (CE-IVD Marked)
- Influenza A virus (Flu A) - Influenza B virus (Flu B) - Respiratory syncytial virus A (RSV A) - Respiratory syncytial virus B (RSV B) - Flu A-H1 - Flu A-H1pdm09 - Flu A-H3	- Adenovirus (AdV) - Enterovirus (HEV) - Parainfluenza virus 1 (PIV 1) - Parainfluenza virus 2 (PIV 2) - Parainfluenza virus 3 (PIV 3) - Parainfluenza virus 4 (PIV 4) - Metapneumovirus (MPV)
Panel 3 (CE-IVD Marked)	**Panel 4 (CE-IVD Marked)**
- Bocavirus (HBoV) - Rhinovirus (HRV) - Coronavirus NL63 (CoV NL63) - Coronavirus 229E (CoV 229E) - Coronavirus OC43 (CoV OC43)	- *Mycoplasma pneumoniae* (MP) - *Chlamydophila pneumoniae* (CP) - *Legionella pneumophila* (LP) - *Haemophilus influenzae* (HI) - *Streptococcus pneumoniae* (SP) - *Bordetella pertussis* (BP) - *Bordetella parapertussis* (BPP)

http://seegene.com/neo/en/products/respiratory/allplex_Rp_fp.php

Laboratory-based:
One-step, sample-to-answer cartridges

https://www.biofiredx.com/

http://www.cepheid.com/

https://www.luminexcorp.com/aries-flu-ab-rsv-assay/

RAPID RESPIRATORY VIRUS DIAGNOSTICS

The Importance of Rapid Diagnosis

Rapid and accurate diagnosis can result in:

- **Less unnecessary antibiotic use**

  (Esposito, et al. *Arch Dis Child* 2003; Blaschke, et al. *J Pediatr Infect Dis Soc* 2014.)

- **Prompt initiation of antiviral therapy**

  (Noyola, et al. *Pediatr Infect Dis* 2000; D'Heilly, et al. *J Clin Virol* 2008)

  Prompt institution of infection control measures, e.g., cohorting to reduce nosocomial transmission

  (Madge, et al. *Lancet* 1990; Mills, et al. *J Hosp Infect* 2011; Caram, et al. *J Am Geriatr Soc* 2009)

- **Fewer hospitalizations or shorter length of stay**

  (Bonner, et al. *Pediatrics* 2003; Nesher, et al. *Infect Contr Hosp Epid* 2019)

- **Fewer ancillary diagnostic tests**

  (Bonner, et al. *Pediatrics* 2003; Iyer, et al. *Acad Emerg Med* 2006)

RSV rapid antigen detection tests (RADT)

- Used by many clinical laboratories in US CDC RSV surveillance program[1]
- **Advantages** related to speed and ease
  - Use at point-of-care (CLIA waived)
- **Major downside**: poor sensitivity:
  - 10-85%

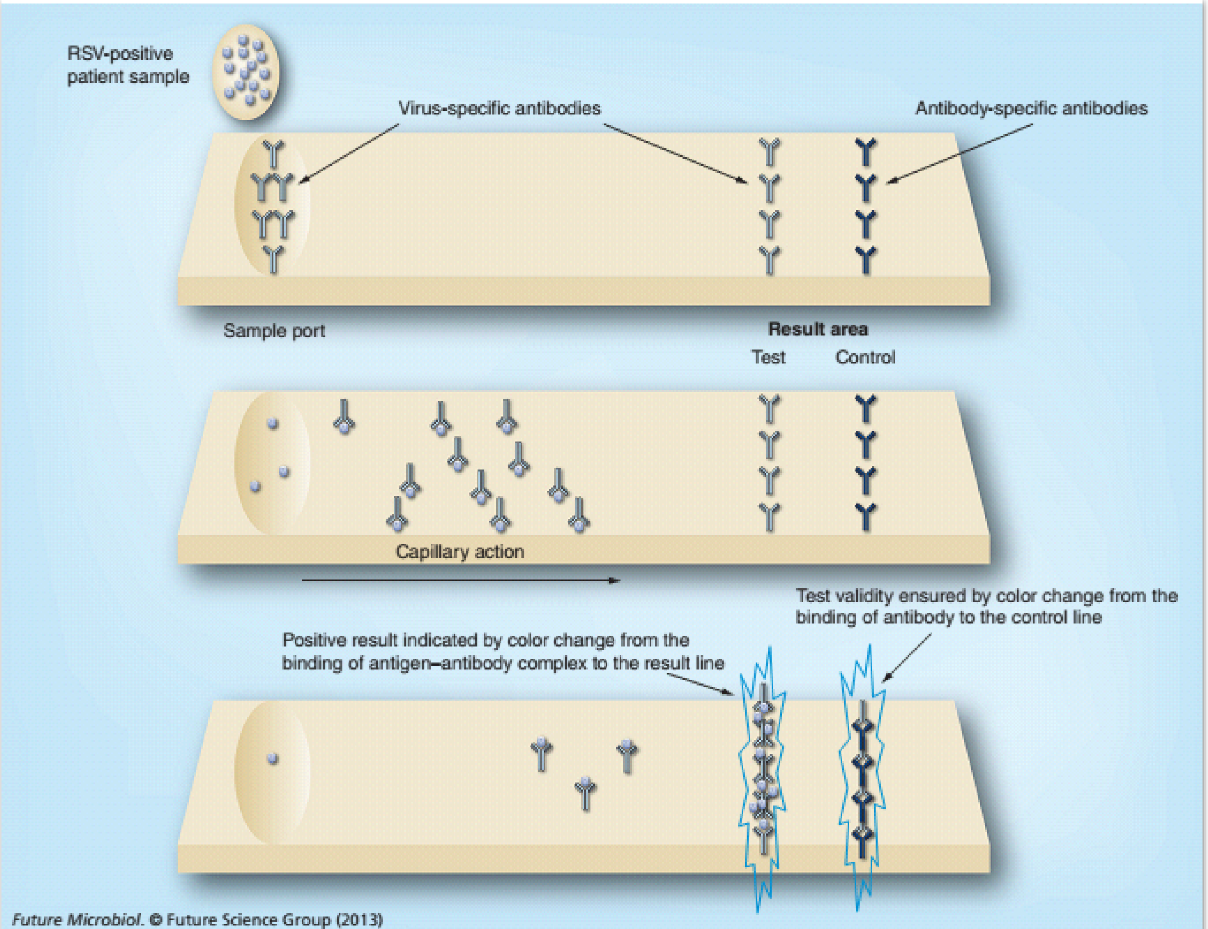


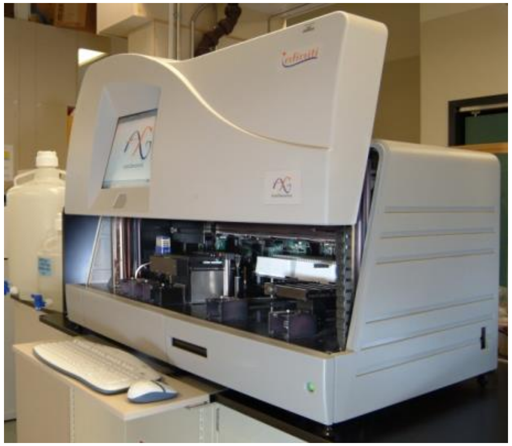
Figure 1. Immunochromatographic rapid diagnostic test for respiratory syncytial virus.
RSV: Respiratory syncytial virus.

1- http://www.cdc.gov/surveillance/nrevss/rsv/
Figure from: Prendergast and Papenburg. *Future Microbiol* 2013

Host and Viral Factors Affecting Clinical Performance of a Rapid Diagnostic Test for Respiratory Syncytial Virus in Hospitalized Children

Jesse Papenburg, MD[1,2], David L. Buckeridge, MD, PhD[1], Gaston De Serres, MD, PhD[3], and Guy Boivin, MD, MSc[4]

J Pediatr. 2013 Sept;163: 911-13



AIM:

To assess factors associated with false-negative RSV RADT in a prospective cohort of 720 children admitted for ARI, of which 463 (64%) were RSV+ by RT-PCR/DNA hybridization assay

Table I. Risk of a false-negative RADT result among 463 hospitalized children <3 years old with RSV RTI confirmed by RT-PCR/DNA hybridization assay

	True positive* n (%)	False negative n (%)	RR (95% CI)	*P* value†
Age (mo)				
0-5	227 (83.8)	44 (16.2)	Ref.	n/a
6-11	61 (79.2)	16 (20.8)	1.28 (0.77-2.14)	.392
12-17	39 (78.0)	11 (22.0)	1.36 (0.75-2.43)	.312
18-23	22 (73.3)	8 (26.7)	1.64 (0.86-3.15)	.199
24-35	21 (60.0)	14 (40.0)	**2.46 (1.52-4.01)**	**.002**
Sex				
Female	156 (79.2)	41 (20.8)	Ref.	n/a
Male	214 (80.5)	52 (19.5)	0.94 (0.65-1.35)	.815
Symptom duration (d)				
<5	285 (82.8)	59 (17.2)	Ref.	n/a
≥5 d	85 (72.0)	33 (28.0)	**1.63 (1.12-2.36)**	**.016**
Fever ≥38.5°C				
No	136 (81.0)	32 (19.0)	Ref.	n/a
Yes	234 (79.3)	61 (20.7)	1.09 (0.74-1.59)	.739
Pneumonia‡				
No	253 (84.1)	48 (15.9)	Ref.	n/a
Yes	117 (72.2)	45 (27.8)	**1.74 (1.22-2.49)**	**.003**
Oxygen therapy				
No	73 (73.7)	26 (26.3)	Ref.	n/a
Yes	297 (81.6)	67 (18.4)	0.70 (0.47-1.04)	.091
PICU admission				
No	350 (79.7)	89 (20.3)	Ref.	n/a
Yes	20 (83.3)	4 (16.7)	0.82 (0.33-2.40)	.798
Genotype§				
RSV-A	212 (84.5)	39 (15.5)	Ref.	n/a
RSV-B	153 (74.3)	53 (25.7)	**1.66 (1.14-2.40)**	**.010**

Papenburg et al. *J Pediatr.* 2013

Significance of false-negative RSV RADTs

Clinical:

- Consider re-testing a negative sample by a more sensitive method (e.g., PCR)

Public health:

- Sensitivity of RADTs must be taken into account when estimating RSV hospitalization rates based on **lab surveillance data**
- Failure to do so: **underestimate the burden of RSV** especially among older children

Table II. Multivariable logistic regression model for the outcome of a false-negative RADT result among 463 hospitalized children <3 years old with RSV RTI confirmed by RT-PCR/DNA hybridization assay

Variable†	aOR (95% CI)
Age 0-5 mo	Ref.
Age 6-11 mo	1.06 (0.54-2.10)
Age 12-17 mo	1.43 (0.67-3.11)
Age 18-23 mo	1.71 (0.67-4.34)
Age 24-35 mo	**3.04** **(1.33-6.95)**
Symptom duration ≥5 d	**2.12** **(1.27-3.57)**
RSV Genotype B	**1.90** **(1.17-3.08)**
Pneumonia*	1.39 (0.83-2.35)

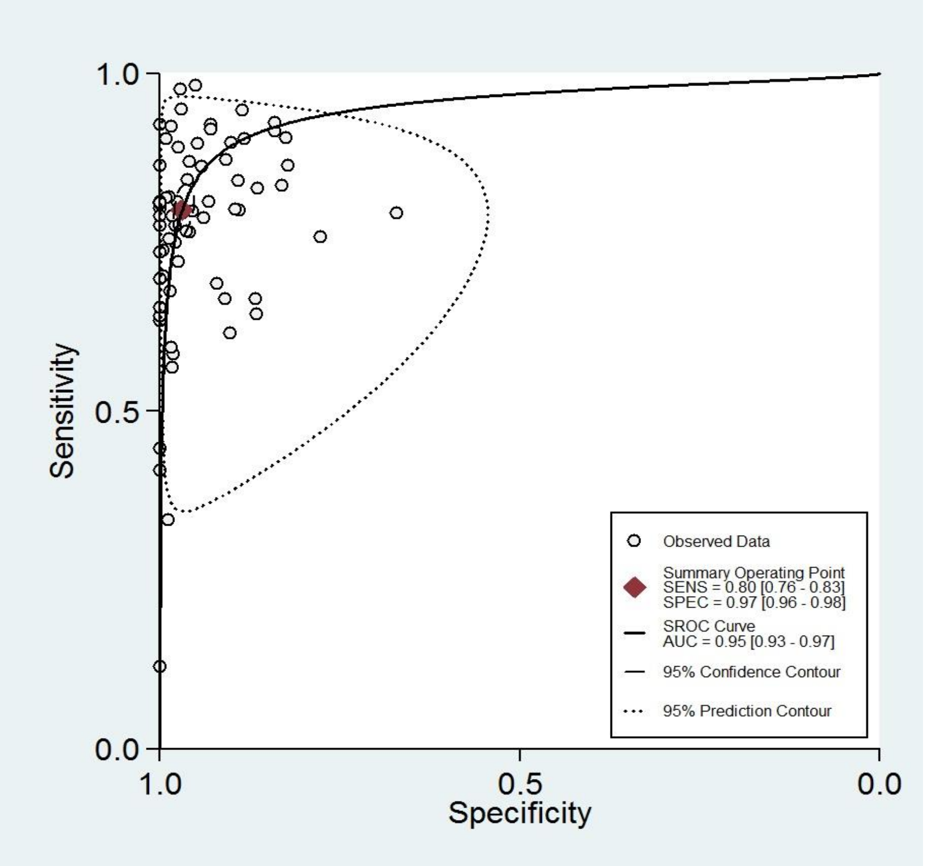
J Pediatr. 2013 Sept;163: 911-13

Systematic review / meta-analysis of RSV RADT diagnostic accuracy

<u>71 studies</u>

Pooled estimates (95%CI)

- **Sens.**: **80%** (76%-83%)
- **Spec.**: **97%** (96%-98%)
- **+LR**: **25.5** (18.3 - 35.5)
- **-LR**: **0.21** (0.18 - 0.24)



Adults:

- Sensitivity 29% (11% - 48%)

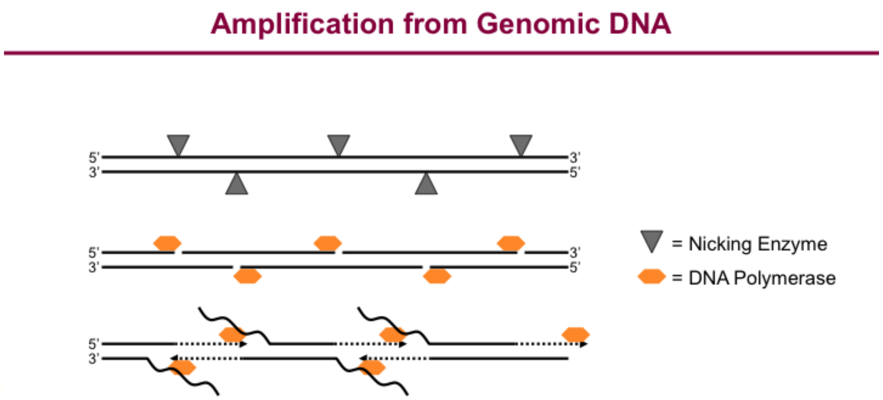
Chartrand et al. *J Clin Microbiol* 2015

Novel rapid diagnostics: influenza and RSV

- **Digital immunoassays (DIAs) with automated reader**
  - BD Veritor™ System Flu A+B *or* RSV
  - (Quidel) Sofia® Influenza A+B *or* RSV

Novel rapid diagnostics: influenza and RSV

- **Rapid nucleic acid amplification tests (NAATs)**
  - Alere™ i Influenza A&B *or* iRSV
  - (Roche) Cobas® Liat Influenza A/B & RSV assay



Novel Rapid Diagnostic Tests for Influenza Approved for Use at the Point of Care

- **Digital immunoassays (DIAs) with automated reader**
  - Veritor System Flu A+B: ~10 minutes
  - Sofia Influenza A+B FIA: ~ 10 minutes
- **Rapid nucleic acid amplification tests (NAATs)**
  - Alere i Influenza A&B: ~13 minutes
  - cobas Liat Influenza A/B and RSV assay: <20 minutes
  - Xpert Xpress Flu/RSV: 20-30 minutes
  - FilmArray Respiratory Panel EZ (14 pathogens): ~ 1hour

New US FDA minimum performance standards for rapid tests (2018)

Sensitivity ≥ 80% with 95% CI lower bound of 70% against RT-PCR reference standard

FDA Fact Sheet. CLIA-Waived Rapid Flu Test Facts. https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM596063.pdf

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REVIEWS | 19 SEPTEMBER 2017

Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction: A Systematic Review and Meta-analysis

Joanna Merckx, MD, MSc; Rehab Wali, BSc, MBBS; Ian Schiller, MSc; Chelsea Caya, MScPH; Genevieve C. Gore, MLIS; Caroline Chartrand, MD, MSc; Nandini Dendukuri, PhD; Jesse Papenburg, MD, MSc

Merckx J, et al. *Ann Intern Med.* 2017;167(6):394-409.

Rapid Test Diagnostic Accuracy: Primary Results

	Influenza A	Influenza B
	Sensitivity, % (95% CrI)	**Sensitivity, % (95% CrI)**
OVERALL		
Traditional RIDTs	54.4 (48.9−59.8)	53.2 (41.7−64.4)
DIAs	80.0 (73.4−85.6)	76.8 (65.4−85.4)
NAATs	91.6 (84.9−95.9)	95.4 (87.3−98.7)
Difference in sensitivities, overall		
DIAs vs. Trad. RIDTs	**25.5 (17.0 − 33.4)**	**23.5 (7.7 − 37.9)**
NAATs vs. Trad. RIDTs	**37.1 (28.6 − 44.2)**	**41.7 (28.5 − 54.0)**
NAATs vs. DIAs	**11.5 (2.9 − 19.5)**	**18.2 (6.9 − 30.6)**

All specificities ≥98.3

RIDTs = rapid influenza diagnostic tests, DIAs = digital immunoassays, NAATs = nucleic acid amplification tests, CrI = credible interval

Merckx J, et al. *Ann Intern Med.* 2017;167(6):394-409.

Subgroup Analysis: Patient Age

	Influenza A	Influenza B
Traditional RIDTs	**Sensitivity, % (95% Crl)**	**Sensitivity, % (95% Crl)**
Children	61.2 (55.0−67.2)	65.7 (45.3−80.5)
Adults	42.6 (34.8−50.9)	33.2 (19.9−50.7)
Difference in RIDT sensitivity: Children vs. Adults		
	18.5 (8.4−28.3)	**31.8 (6.1−52.6)**
DIAs		
Children	87.6 (81.8−92.2)	82.5 (71.2−90.2)
Adults	75.4 (66.6−82.6)	57.0 (39.5−71.6)
Difference in DIA sensitivity: Children vs. Adults		
	12.1 (3.1−22.1)	**25.3 (6.9−44.7)**
NAATs		
Children	90.2 (79.2−95.8)	95.9 (82.9−99.2)
Adults	87.4 (71.1−95.6)	75.7 (51.8−90.7)
Difference in NAAT sensitivity: Children vs. Adults		
	2.7 (-10.7−19.7)	**19.5 (1.0−43.7)**

Merckx J, et al. *Ann Intern Med.* 2017;167(6):394-409.

Subgroup Analysis: Commercial Brand

	Influenza A	Influenza B
	Sensitivity, % (95% Crl)	**Sensitivity, % (95% Crl)**
DIAs		
Sofia Influenza A+B FIA (n=12)	77.8 (68.8−85.4)	73.5 (55.8−86.1)
Veritor Flu A+B (n=6)	83.0 (73.4−90.1)	80.0 (68.8−88.2)
Difference in DIA sensitivity: BD Veritor vs. Sofia		
	5.1 (-6.9−16.4)	6.4 (-10.4−25.8)
NAATs		
Alere i Influenza A&B (n=7)	84.4 (75.3−90.9)	86.6 (69.0−95.3)
Cobas Liat Influenza A/B (n=5)	97.1 (92.9−98.9)	98.7 (95.6−99.7)
Difference in NAAT sensitivity: Cobas Liat vs. Alere i		
	12.4 (4.9−21.9)	**11.8 (2.8−29.5)**

Merckx J, et al. *Ann Intern Med.* 2017;167(6):394-409.

EDITORIAL

Annals of Internal Medicine

Contemporary Influenza Diagnostics: Renewed Focus on Testing Patients

- "a clear need to improve appropriate early access to antiviral therapy and to reduce inappropriate antibacterial use in patients with influenza"
- "The data provided in Merckx and colleagues' review should prompt revision of guidelines to encourage use of these newer diagnostic strategies. Although studies are needed to confirm the utility of these assays in the point-of-care setting and to optimize their implementation and use, the strength of the data suggests that now is the time to utilize these newer tests to help clinicians make better antimicrobial choices for patients with influenza infection."

Ison MG. *Ann Intern Med*. 2017;167(6):438-9

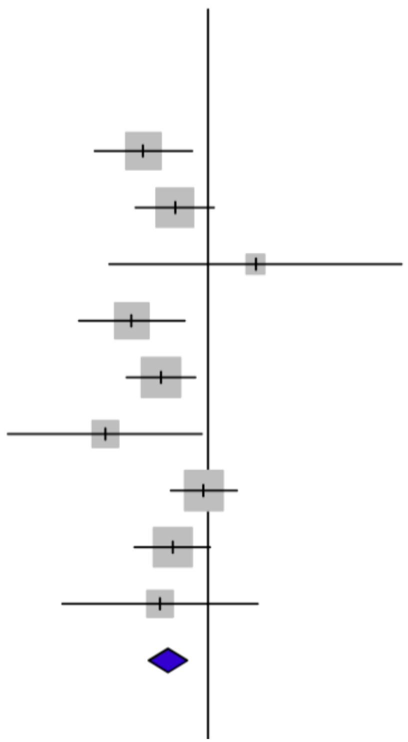
CLINICAL IMPACT OF DIAGNOSTIC TESTING

The Clinical Utility of Respiratory Viral Testing in Hospitalized Children: a Meta-Analysis

Figure 4. Subgroup analysis by study design. Forest plot of the pooled OR comparing the proportion of patients receiving antibiotics among those with a positive *vs.* negative RV test result. Test for subgroup differences: p = 0.02.

	VIRUS(+)		VIRUS(-)			
Study	**Events**	**Total**	**Events**	**Total**	**OR**	**95%-CI**
Prospective cohort study						
Adcock 1997	40	92	44	68	0.42	[0.22; 0.80]
Bozdemir 2016	224	254	384	417	0.64	[0.38; 1.08]
Bueno 2012	6	8	8	13	1.88	[0.27; 13.20]
Hatipoglu 2011	26	54	67	93	0.36	[0.18; 0.73]
Manji 2009	46	85	357	518	0.53	[0.33; 0.85]
Nitsch-Osuch 2016	3	64	14	86	0.25	[0.07; 0.92]
Suntarattiwong 2011	77	130	136	224	0.94	[0.60; 1.46]
Tsung 2010	30	234	45	235	0.62	[0.38; 1.03]
van de Pol 2010	9	19	12	19	0.52	[0.14; 1.92]
Random effects model		940		1673	0.58	[0.45; 0.75]

Heterogeneity: $I^2 = 25\%$, $\tau^2 = 0.0360$



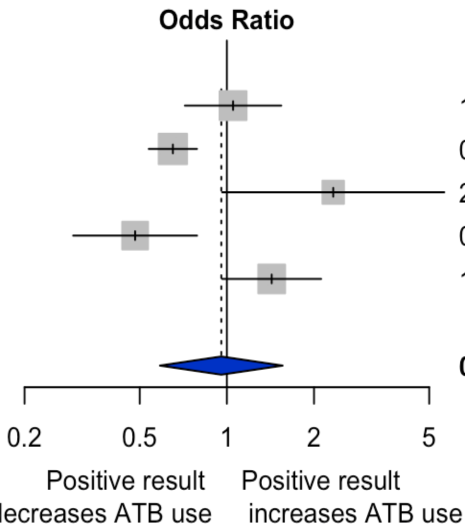
Noel et al, *Hosp Pediatrics* 2019

The Clinical Utility of Respiratory Viral Testing in Hospitalized Children: a Meta-Analysis

Pooled OR of studies with 100% bronchiolitis patients

Study	VIRUS(+) Events	VIRUS(+) Total	VIRUS(-) Events	VIRUS(-) Total	OR	95%-CI	Weight
Azzarone 2012	71	183	105	279	1.05	[0.72; 1.54]	21.5%
Flaherman 2010	384	971	379	756	0.65	[0.54; 0.79]	23.8%
Milić 2017	122	134	48	59	2.33	[0.96; 5.64]	13.7%
Paul 2017	76	227	47	92	0.48	[0.29; 0.79]	19.7%
Tsolia 2003	113	291	56	182	1.43	[0.96; 2.12]	21.3%
Random effects model		**1806**		**1368**	**0.96**	**[0.59; 1.56]**	**100.0%**

Heterogeneity: $I^2 = 84\%$, $\tau^2 = 0.2507$



Noel et al, *Hosp Pediatrics* 2019

Multiplex Respiratory Virus Testing for Antimicrobial Stewardship: A Prospective Assessment of Antimicrobial Use and Clinical Outcomes Among Hospitalized Adults

Makeda Semret,[1] Ian Schiller,[2] Barbara Ann Jardin,[2] Charles Frenette,[1] Vivian G. Loo,[1] Jesse Papenburg,[1] Shelly A. McNeil,[4] and Nandini Dendukuri[3]

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- Secondary analysis of prospective cohort of 800 adults admitted with suspected respiratory infection at MUHC
- Antibiotic management was significantly associated with radiographic pneumonia, **not results of multiplex RV test**
- ~ 8-fold increase in appropriateness of antiviral treatment based on influenza results

Semret el al. *J Infect Dis* **2017**

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Viral Diagnostics: Only Half the Battle

Angela R. Branche[1] and Ann R. Falsey[1,2,3]

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(See the major article by Semret et al, on pages 936–44.)

- What's missing?
  - Use of rapid tests?
  - Biomarkers to reduce uncertainty regarding bacterial co-infection?
  - Antimicrobial stewardship programs?
  - Choosing (wisely) your patient population, setting and clinical syndrome?
  - Reducing unnecessary chest radiography?

Branche and Falsey. *J Infect Dis* **2017**

FULL TEXT ARTICLE

Procalcitonin and antibiotic use: imperfect, yet effective

Patricia S Fontela and Jesse Papenburg

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Summary

- Modern respiratory virus testing is simpler, faster, more accurate and more multiplexed
- To leverage these technological advances and improve patient outcomes, we need to "choose wisely"
- Evidence shows challenges for real-world implementation