European Academy of Paediatrics
Paediatric Section of U.E.M.S

Influenza POCT in paediatric primary care. Any Benefits?

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Scientific Session of the winter meeting of the European Academy of Paediatrics.

Burden of disease

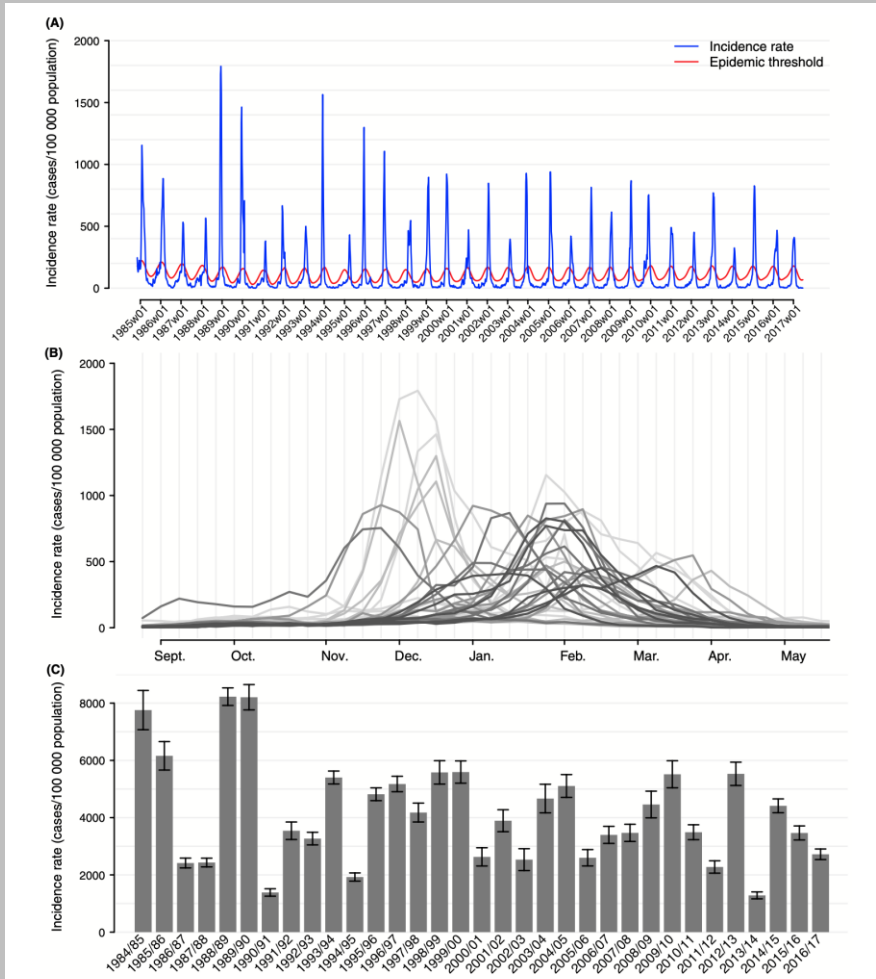


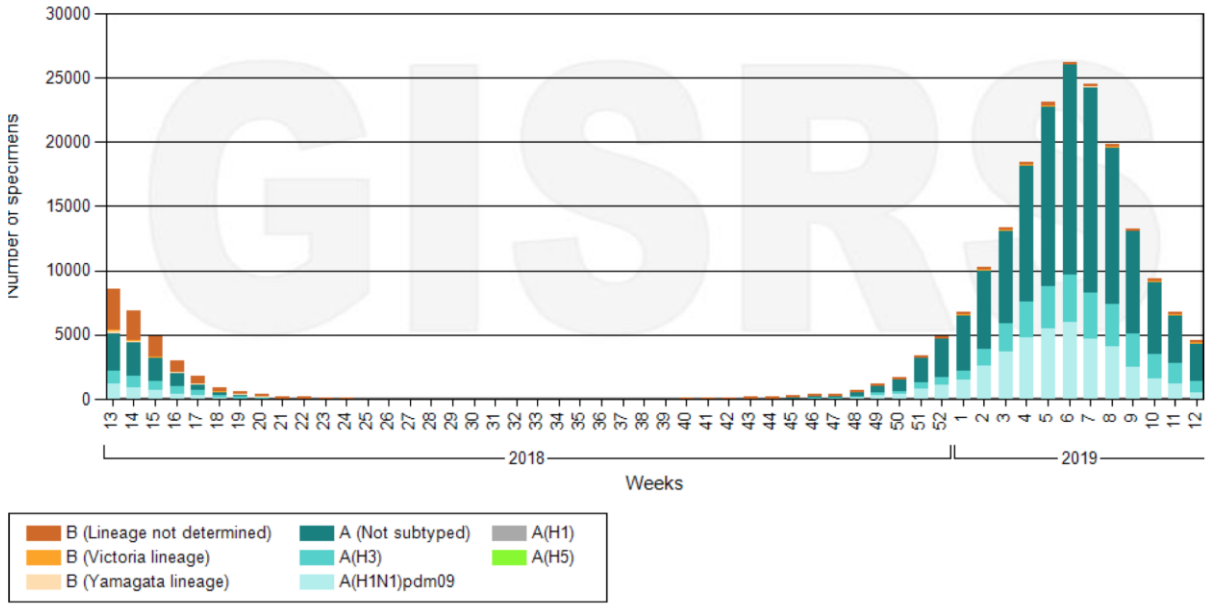
FIGURE 1 Incidence of influenza-like illness estimated per 100 000 population between 1984 and 2017; (A) weekly continuous series; (B) layered epidemic (the clearer the line, the older the epidemic); (C) cumulative ILI incidence rate by epidemic and 95% confidence intervals, *Sentinelles* network, France

Souty C, et al. Influenza epidemics observed in primary care from 1984 to 2017 in France. ***Influenza Other Respi Viruses.*** **2019;13:148–157.**

Burden of disease

World Health Organization

Number of specimens positive for influenza by subtype in the European Region of WHO



Data source: FluNet (www.who.int/flunet). Global Influenza Surveillance and Response System (GISRS)
Data generated on 29/03/2019

Source: FluNet. Global Influenza Surveillance and Response System (GISRS)

Burden of disease

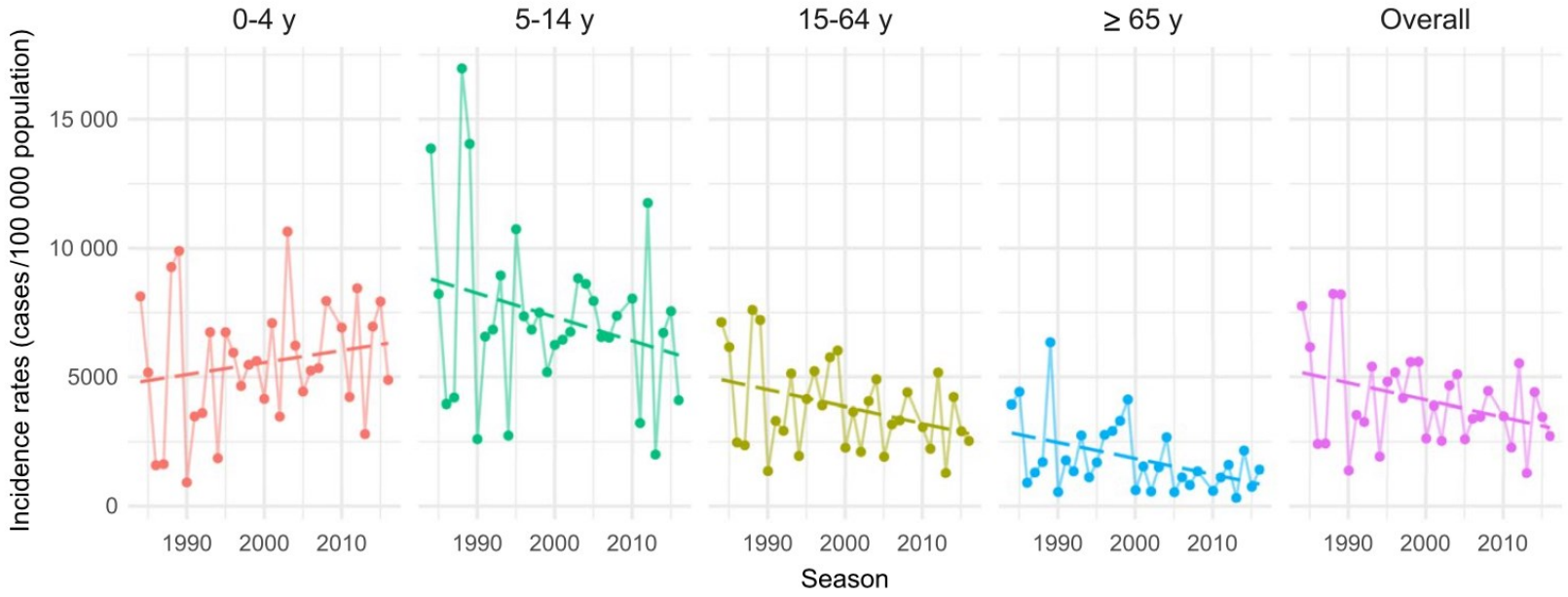
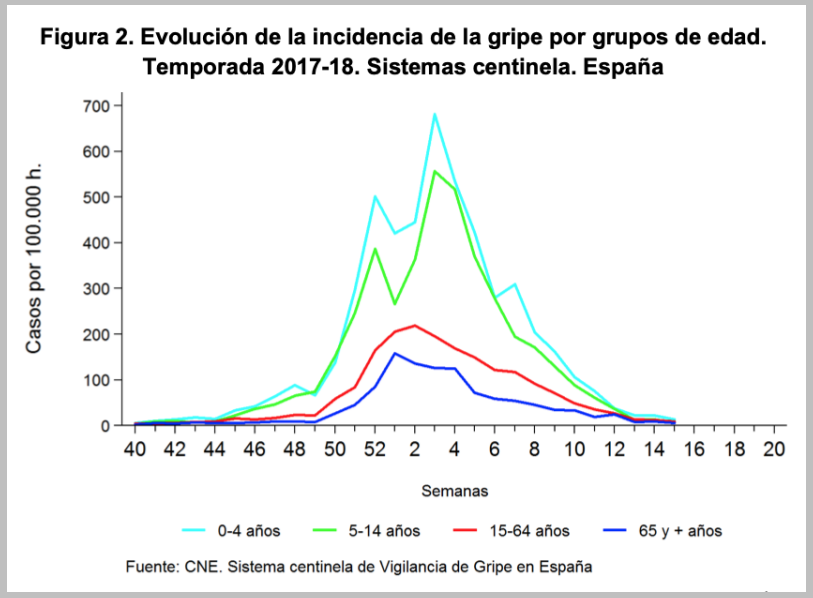
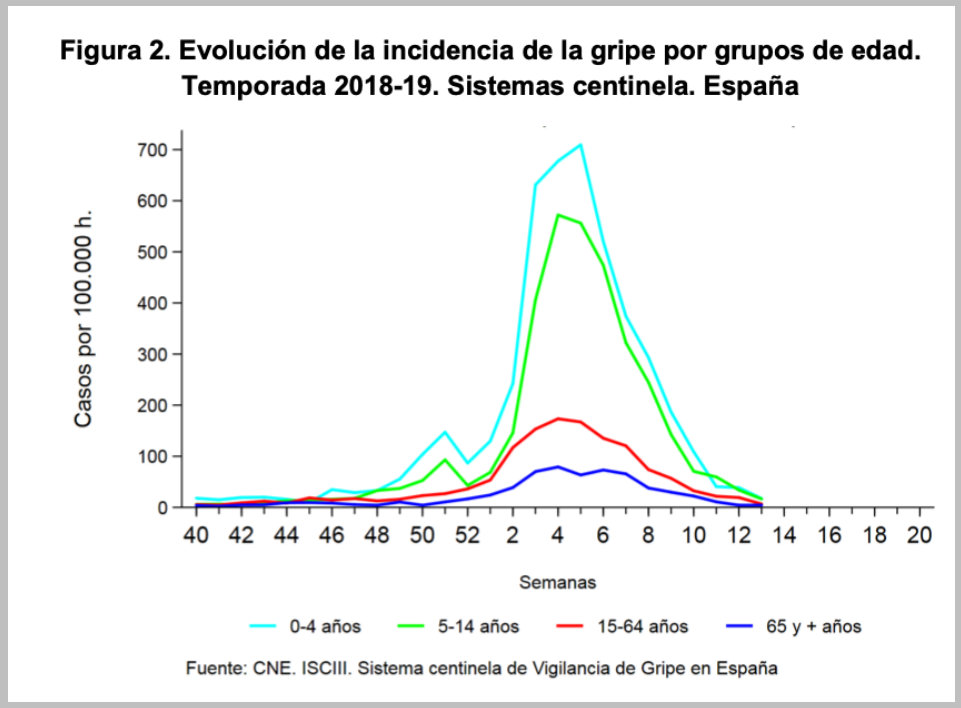


FIGURE 2 Incidence of influenza-like illness estimated per 100 000 population by epidemic for four age groups and overall, with linear regression lines, from 1984/85 to 2016/17, *Sentinelles* network, France

Souty C, et al. Influenza epidemics observed in primary care from 1984 to 2017 in France. ***Influenza Other Respi Viruses.*** **2019;13:148–157.**

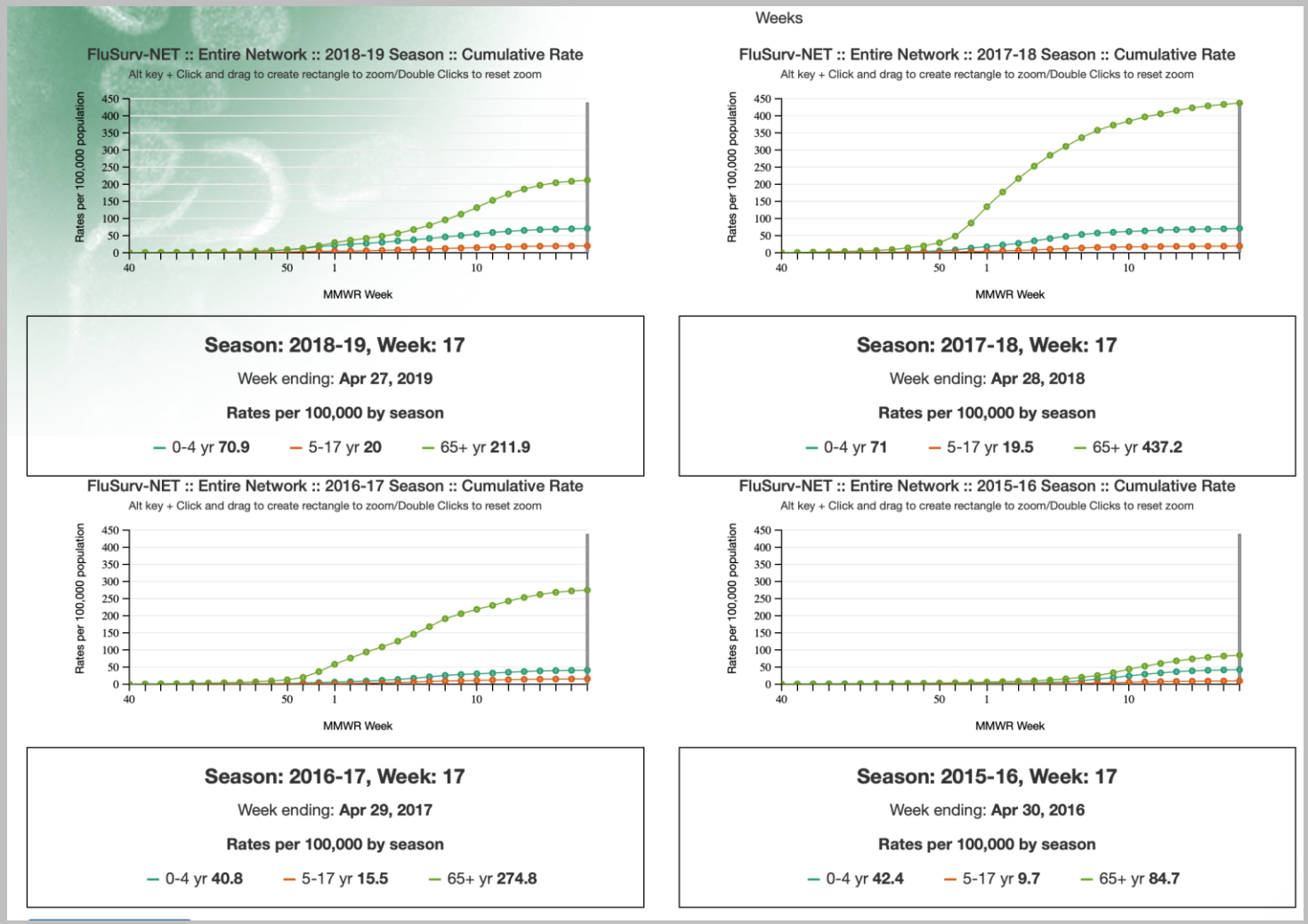
Burden of disease by age group





Source: National Center of Epidemiology (Spain). Centinel Influenza Surveillance System. Season 2017-18 and 2018-19

Burden of disease: hospitalization

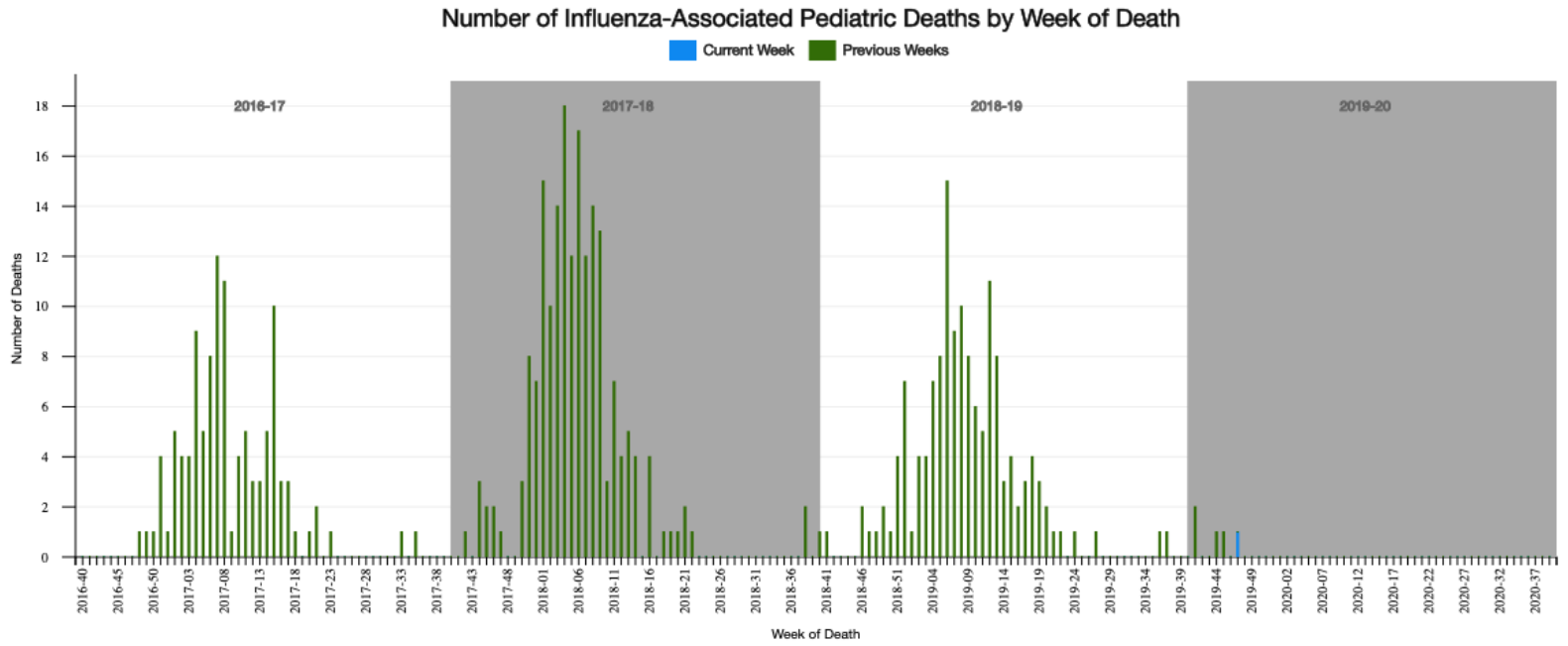


Source: FluView. CDC.

Burden of disease. Infant mortality

FluView

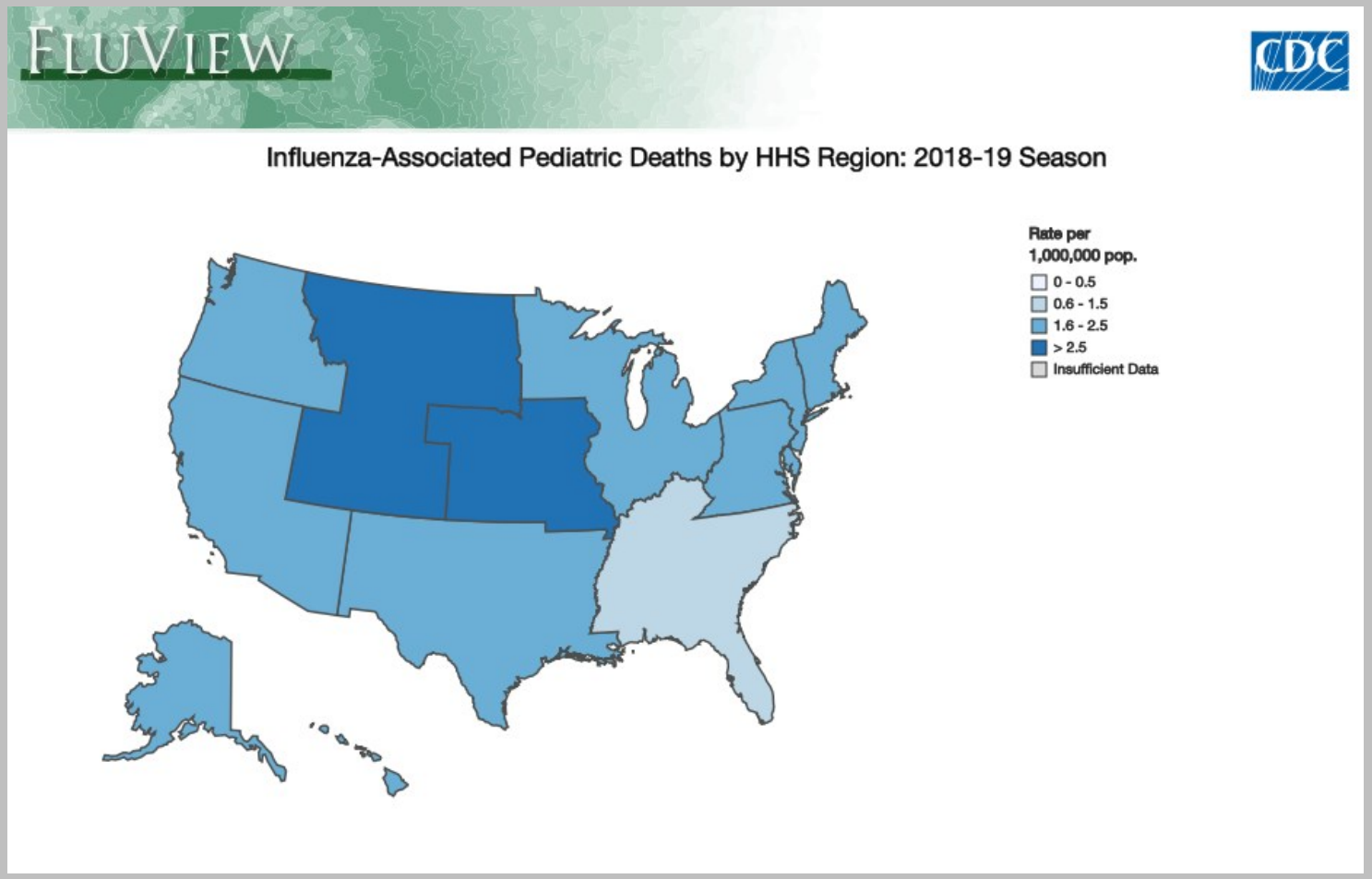
CDC



Seasons	Total Deaths	Deaths reported During the Week Ending 23 Nov 2019
2016-17	110	0
2017-18	187	0
2018-19	143	0
2019-20	5	1

Source: FluView. CDC.

Burden of disease. Infant mortality



Source: FluView. CDC.

Clinical diagnosis. Recognizing influenza in children in primary care.

Definition of ILI according to CDC: fever > 37.8 ℃ and cough and/ore sore throat in the absence of known cause other than influenza

Definition of ILI according to WHO: Acute respiratory infection with measured fever ≥ 38.0 ℃ and cough with onset within the last 10 days

The sensitivity of the clinical diagnosis of influenza is only 38% and the positive predictive value (32%). Peltola

Peltola et a. (2005) Clin Infect Dis 41:1198-1200

Clinical symptoms. Recognizing influenza in children 0-6 yr as outpatients.

- Fever ≥ 37.5°C **(91%)**
- Fever ≥ 39.0°C **(52%)**
- Fever ≥ 40.0°C **(12%)**
- Rhinitis **(76%)**
- Cough **(73%)**
- Sore throat **(14%)**
- Headache **(11%)**
- Myalgia **(2%)**
- Gastrointestinal symptoms **(8%)**
- Impaired general condition **(9%)**
- Conjunctivitis **(7%)**

No major differences between Influenza A and B.

Silvennoinen H, et al. Clinical presentation of Influenza in Unselected Children. **Pediar Infect Dis J. 2009;28:372-375.**

Duration of symptoms. Paediatric primary care patients 0-6 y. mean duration of symptoms (days)

- Fever **5.6**
- Rhinitis **8.5**
- Cough **7.70**
- Irritability **3.11**
- Headache **0.83**
- Myalgia **1.10**
- Gastrointestinal symptoms **0.76**
- Impaired general condition / Anorexia: **4.44**

Van Esso et al. (2019). Unpublished data

Summary

- Influenza is frequent in children. They have, as a group, the highest infection rate.

- Clinical diagnosis of influenza is very difficult especially in young children.
- Classic symptoms as headache and myalgia, frequently present in adults, are absent or difficult to asses in young children.
- Symptoms last longer than a few days.

- Children are submitted to laboratory tests, X-rays and hospital admissions usually for high fever with out other major symptoms.

- A microbiologic confirmation in primary care is warranted, at least in some occasions, in the lowest age group.

The microbiologic test

Microbiologic test. Where?

- In primary care if you ask the lab for a influenza diagnostic test it may take, in the best scenario, 2-3 days to get the result.
- Patients can go to the hospital (or site where a PCR test is available) and get a result in the same day or next day. Is this reasonable?
- Patient can be diagnosed with a POCT and get the result in 15 minutes or less.

Rapid Influenza Diagnostic Tests (POCTs)

Index Test Type	Influenza A		Influenza B	
	Pooled Sensitivity (95% CrI), %	**Pooled Specificity (95% CrI), %**	**Pooled Sensitivity (95% CrI), %**	**Pooled Specificity (95% CrI), %**
Subgroup analyses†				
Study population (age)‡				
Traditional RIDTs				
Children (31 influenza A studies; 9 influenza B studies)	61.2 (55.0 to 67.2)	99.2 (98.5 to 99.7)	65.7 (45.3 to 80.5)	99.6 (99.2 to 99.8)
Adults (23 influenza A studies; 5 influenza B studies)	42.6 (34.8 to 50.9)	99.5 (98.6 to 99.8)	33.2 (19.9 to 50.7)	99.9 (99.4 to 100)
Difference in RIDT sensitivity: children vs. adults	**18.5 (8.4 to 28.3)**	–	**31.8 (6.1 to 52.6)**	–
DIAs				
Children (11 influenza A studies; 11 influenza B studies)	87.6 (81.8 to 92.2)	98.1 (96.4 to 99.1)	82.5 (71.2 to 90.2)	98.8 (95.6 to 99.7)
Adults (8 influenza A studies; 7 influenza B studies)	75.4 (66.6 to 82.6)	96.7 (94.7 to 98.0)	57.0 (39.5 to 71.6)	98.8 (97.5 to 99.5)
Difference in DIA sensitivity: children vs. adults	**12.1 (3.1 to 22.1)**	–	**25.3 (6.9 to 44.7)**	–
Rapid NAATs				
Children (4 influenza A studies; 4 influenza B studies)	90.2 (79.2 to 95.8)	99.0 (96.8 to 99.8)	95.9 (82.9 to 99.2)	99.5 (98.2 to 99.9)
Adults (4 influenza A studies; 4 influenza B studies)	87.4 (71.1 to 95.6)	98.0 (93.2 to 99.5)	75.7 (51.8 to 90.7)	99.3 (97.8 to 99.8)
Difference in NAAT sensitivity: children vs. adults	2.7 (−10.7 to 19.7)	–	**19.5 (1.0 to 43.7)**	–

Merckx J, et al. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection.... A Systematic Review and Meta-analysis. *Ann Intenn Med.* 2017;167:394-409. DOI: 10.7326/M17-0848

Rapid Influenza Diagnostic Tests (POCTs)

Table 2. Overall and Subgroup Analyses of Pooled Rapid Test Accuracy Estimates for Influenza A and B, by Index Test Type*

Index Test Type	Influenza A		Influenza B	
	Pooled Sensitivity (95% CrI), %	**Pooled Specificity (95% CrI), %**	**Pooled Sensitivity (95% CrI), %**	**Pooled Specificity (95% CrI), %**
Overall				
Traditional RIDTs (94 influenza A studies; 30 influenza B studies)	54.4 (48.9 to 59.8)	99.4 (99.1 to 99.7)	53.2 (41.7 to 64.4)	99.8 (99.7 to 99.9)
DIAs (18 influenza A studies; 17 influenza B studies)	80.0 (73.4 to 85.6)	98.3 (97.4 to 98.9)	76.8 (65.4 to 85.4)	98.7 (97.5 to 99.4)
Rapid NAATs (12 influenza A studies; 12 influenza B studies)	91.6 (84.9 to 95.9)	99.2 (98.6 to 99.7)	95.4 (87.3 to 98.7)	99.4 (98.9 to 99.8)
Difference in sensitivities, overall				
Traditional RIDTs vs. DIAs	**−25.5 (−33.4 to −17.0)**	-	**−23.5 (−37.9 to −7.7)**	-
Traditional RIDTs vs. rapid NAATs	**−37.1 (−44.2 to −28.6)**	-	**−41.7 (−54.0 to −28.5)**	-
DIAs vs. rapid NAATs	**−11.5 (−19.5 to −2.9)**	-	**−18.2 (−30.6 to −6.9)**	-

Merckx J, et al. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection.... A Systematic Review and Meta-analysis. *Ann Intenn Med.* 2017;167:394-409. DOI: 10.7326/M17-0848

Rapid Influenza Diagnostic Tests (POCTs)

Index Test Type	Influenza A		Influenza B	
	Pooled Sensitivity (95% CrI), %	**Pooled Specificity (95% CrI), %**	**Pooled Sensitivity (95% CrI), %**	**Pooled Specificity (95% CrI), %**
Commercial brand				
DIAs				
Sofia (12 influenza A studies; 11 influenza B studies)	77.8 (68.8 to 85.4)	98.5 (97.4 to 99.2)	73.5 (55.8 to 86.1)	98.0 (95.4 to 99.1)
Veritor (6 influenza A studies; 6 influenza B studies)	83.0 (73.4 to 90.1)	97.5 (95.5 to 98.7)	80.0 (68.8 to 88.2)	99.5 (98.8 to 99.8)
Difference in DIA sensitivity: Sofia vs. Veritor	−5.1 (−16.4 to 6.9)	-	−6.4 (−25.8 to 10.4)	-
Rapid NAATs				
Alere (7 influenza A studies; 7 influenza B studies)	84.4 (75.3 to 90.9)	98.9 (97.7 to 99.6)	86.6 (69.0 to 95.3)	99.1 (98.1 to 99.7)
Liat (5 influenza A studies; 5 influenza B studies)	97.1 (92.9 to 98.9)	99.4 (98.4 to 99.8)	98.7 (95.6 to 99.7)	99.5 (98.7 to 99.9)
Difference in NAAT sensitivity: Alere vs. Liat	**−12.4 (−21.9 to −4.9)**	-	**−11.8 (−29.5 to −2.8)**	-

Merckx J, et al. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection.... A Systematic Review and Meta-analysis. *Ann Intenn Med.* 2017;167:394-409. DOI: 10.7326/M17-0848

Things we know…

- The so called Influenza –like illness (ILI) includes many different viral respiratory diseases and therefore is not very precise if we want to diagnose **influenza**.
- Influenza clinical diagnosis is not as easy as in paediatric patients due to reduced capability to explain some of the key symptoms.
- Diagnostic uncertainty has (nowadays) consequences.
  - Contributes to antibiotic prescription (Ashdown)
  - 14-40% of patients with influenza are prescribed antibiotics (Ciesla G, Ebell MH).
  - Parents with a child with high fever seek advise more than once if they do not get a clear diagnosis. (van Esso)

- New generation Influenza POCTs have high specificity and adequate sensitivity and are adequate for use in primary care POC. (Merckx).
- The proposed criteria for an ideal diagnostic POCT in PID have been published (Keitel K, et al.)

Lee JJ, et al. The Clinical Utility of Point-of-Care Tests for Influenza in Ambulatory Care: A Systematic Review and Meta-analysis. CID 2019;69:24-33. Keitel K, et al. Point of Care testing in Pediatric Infectious Disease. ESPID Reports and Reviews Pediatr Infect Dis Journal 2018;37:108-110

Things we do not know… and therefore need more high quality research

- How an Influenza POCT will change clinical practice at different point-of-care levels
  - Emergency departments.
  - Outpatients clinics.
  - Primary care.
- How an Influenza POCT will change clinical practice if used in different Health Care Systems.
- How an Influenza POCT will change clinical practice if used in different age groups.
- Is classic academic definition of usefulness of a POCT in terms of modifying the treatment of the patient valid, or is it consequence of expert bias?

Potential benefits of Influenza POCT in paediatric primary care.

- **Confirmation of a probable clinical diagnosis.**
- Recognize bacterial infections as secondary infections of influenza.
- **Additional visits in primary care. Returning for follow up.**
- **Antibiotic prescription.**
- Antiviral prescription.
- **Management of the patient.**
- Further laboratory and /or X-rays.
- Hospital admission.
- **Relationship between primary care provider and families.**
- **Surveillance. Real time information.**

RAPID INFLUENZA TESTING IN INFANTS AND CHILDREN YOUNGER THAN 6 YEARS IN PRIMARY CARE

IMPACT ON ANTIBIOTIC TREATMENT AND USE OF HEALTH SERVICES

Diego L. van Esso, MD, Ana Marta Valente, MD,† Monica Vilà, PhD,‡ Josep M. Casanovas, MD,§ Marta de Quixano, MD,¶ Carlos Rodrigo, PhD,‖ ** Andres Anton, PhD,†† and Tomas Pumarola, PhD‡‡*

Abstract: Influenza is often misdiagnosed in children because of the low sensitivity of clinical diagnosis because of nonspecific signs and symptoms. This can be overcome by using digital immunoassays or rapid molecular diagnostic tests with adequate sensitivity and specificity. When using these tests at the patient care site, antibiotic consumption and number of health-care consultations were reduced.

Key Words: influenza, primary care, children, rapid influenza diagnostic test, point of care test

TABLE 1. Comparison of Antibiotic Treatment and Additional Visits in Primary Care

	Group 1*	Group 2†	Group 3‡	*P*§ (Group 1 vs. Group 2)	*P*§ (Group 1 vs. Group 3)
Number of subjects	91	166	913	—	—
Age mean, (SD; range), mo	31.2 (16.5; 4–60)	34.0 (16.7; 6–60)	29.1 (17.2; 6–60)	0.23	0.24
Antibiotic treatment (%)	4.4	7.2	9.7	0.38	0.098
Additional visits in primary care	0.19	0.48	0.81	0.001	<0.001

*Group 1: Influenza-confirmed diagnosis.

†Control group 2: Influenza clinical diagnosis (J11).

‡Control group 3: Clinical diagnosis (J11, B34 and R50).

§$P < 0.05$ is significant.

International Classification of Diseases, 10th revision, 2016 coding is as follows: J11: influenza, virus, not identified; B34: viral infection of unspecified site; R50: fever of other and unknown origin.

Type of Test	Sensitivity	Specificity	PPV	NPV
Sofia® Influenza A+B (Quidel)	**93.9%** (95% CI: 86.3–98.0)	**100%** (95% CI: 95.7–100)	**100%** (95% CI: 100–100)	**94.3%** (95% CI: 87.7–97.5)
Cobas® Liat® (Roche)	**97.5%** (95% CI: 91.4-99.7)	**98.8%** (95% CI: 93.5–100	**98.8%** (95% CI: 91.8–99.8),	**97.6%** (95% CI: 91.3–99.4)

Comparison test was Allplex® RT-PCR

The importance of rapid influenza testing in paediatric primary care: experience during three consecutive influenza seasons (2016-2019) in Barcelona (Catalonia, Spain). van Esso D, et al. **Submitted paper. Under review.**

TABLE 2. Comparison of antibiotic treatment and additional visits in primary care in the different influenza diagnosis groups

	Group 1*		Group 2¥		Group 3§		*P* Group 1 vs Group 2		*P* Group 1 vs Group 3	
	2016-2017	2017-2018	2016-2017	2017-2018	2016-2017	2017-2018	2016-2017	2017-2018	2016-2017	2017-2018
n° subjects	91	343	166	769	253	1029				
Age, months: mean, (SD; range)	31.2 (16.5; 4-60)	35.9 (18.6; 2-72)	34.0 (16.7; 6-60)	39.8 (19.1; 1-72)	27.3 (17.4; 6-60)	32.1 (20.4; 0-72)	0.23	0.002	0.07	0.002
Antibiotic treatment (%)	4.4	10.2	7.2	8.1	11.5	17.2	0.38	0.24	0.052	0.002
Additional visits in primary care	0.19	0.23	0.48	0.49	1.01	0.80	0.001	<0.001	<0.001	<0.001

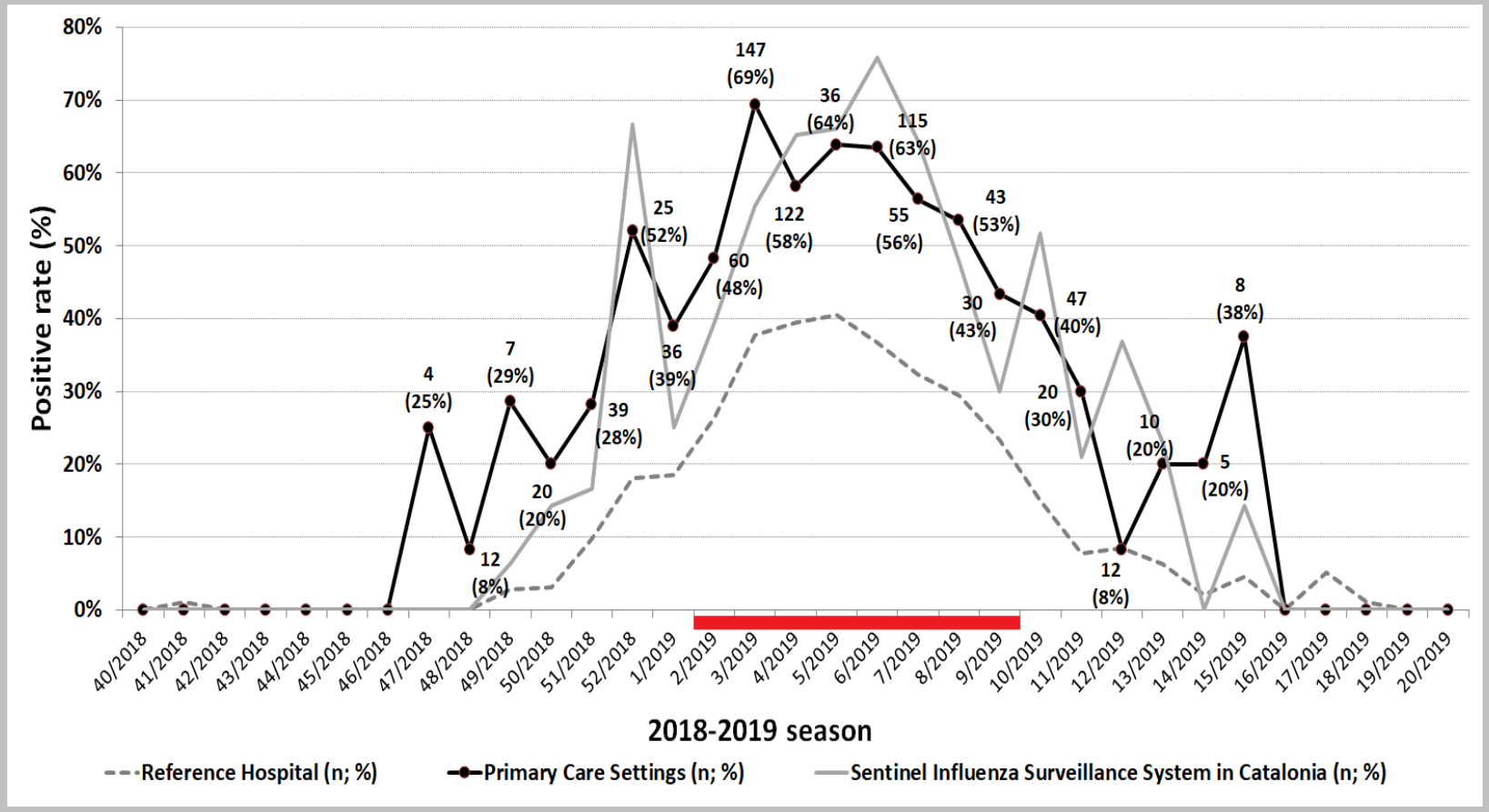
*Group 1: Influenza according to results of RT-PCR confirmation after RIDT.
¥ Control group 2: Influenza clinical diagnosis (J11).
§ Control group 3: Diagnosis of fever (R50).
γ $P < 0.05$ is significant.
ICD10 2016 coding: J11: Influenza, virus, not identified; R50: Fever of other and unknown origin.
Note: Results of first season (N=91) are based on final PCR, while results of second season (N=343) are based on Sofia® test.

The importance of rapid influenza testing in paediatric primary care: experience during three consecutive influenza seasons (2016-2019) in Barcelona (Catalonia, Spain). van Esso D, et al. **Submitted paper. Under review.**

TABLE 3. Sofia® vs Allplex®, sensitivity, specificity, PPV, NPV, diagnostic accuracy, and Kappa values

Targets	N°	Sensitivity		Specificity		PPV		NPV		Diagnostic accuracy		Kappa		Agreement
		Value (%)	95% CI (%)	Value (%)	95% CI (%)	Value (%)	95% CI (%)	Value (%)	95% CI (%)	Value (%)	95% CI (%)	Value (%)	95% CI (%)	
Influenza A	191	**91.0**	86.2 – 94.5	**97.0**	94.8 – 98.4	**94.1**	90.1 – 96.5	**95.2**	93.0 – 96.9	94.9	92.9 – 96.5	0.887	0.848 – 0.925	Excellent
Influenza B	137	**74.4**	67.5 – 80.6	**98.6**	97.0 – 99.5	**95.8**	91.1 – 98.1	**89.9**	87.5 – 92.0	91.3	88.8 – 93.4	0.780	0.724 – 0.836	Good

The importance of rapid influenza testing in paediatric primary care: experience during three consecutive influenza seasons (2016-2019) in Barcelona (Catalonia, Spain). van Esso D, et al. **Submitted paper. Under review.**



Potential benefits of Influenza POCT in paediatric primary care.

- **Additional visits in primary care. Returning for follow up.**
- **Antibiotic prescription.**
- **Confirmation of a clinical diagnosis.**
- **Management of the patient.**
- **Relationship between primary care provider and families.**
- **Surveillance. Real time information.**

Benefits of Influenza POCT in paediatric primary care.

- **Additional visits in primary care. Returning for follow up.**
  - Our group has confirmed in 2 consecutive season that there is a statistically significant reduction when a POCT is used compared to patients with a clinical diagnosis of influenza or a diagnosis of “fever”.

- **Antibiotic prescription.**
  - Our group could find a reduction comparing influenza patients with patients with a diagnosis of fever. In one season this reduction was statisticaly significant and in the previous one it was not.
  - The reduction in antibiotic prescription may depend on baseline prescription habits and other factors which include severity of the influenza season, reliability of the result of the test, different provider visiting the patient in different settings, results of other tests as C-reactive protein, etc.

Benefits of Influenza POCT in paediatric primary care.

- **Confirmation of a clinical diagnosis.**
- **Management of the patient.**
- **Relationship between primary care provider and families.**
  - **Here we have more expert opinions than real world data which are difficult to collect.**
    - **Is it important for parents of a 2 year old child with high fever for 2 days who has a cough to give a clear diagnosis of influenza A or B, explain the duration of the symptoms the possible complications and the need of no treatment except antipyretics? The answer is YES, YES and YES for the 3 potential benefits discussed here.**

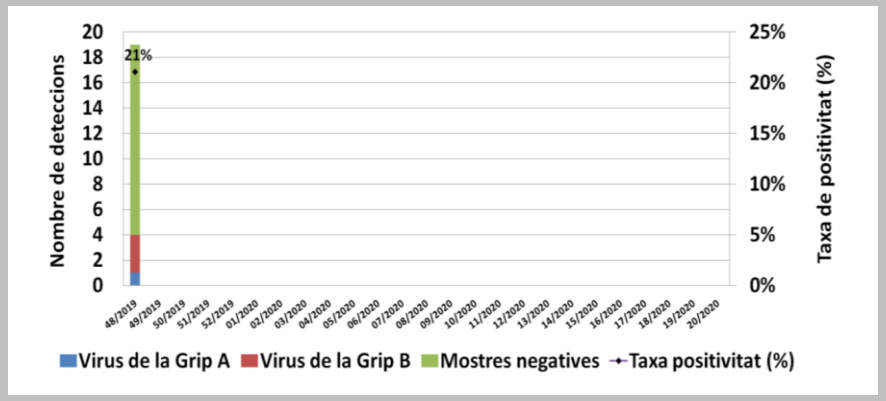
Benefits of Influenza POCT in paediatric primary care.

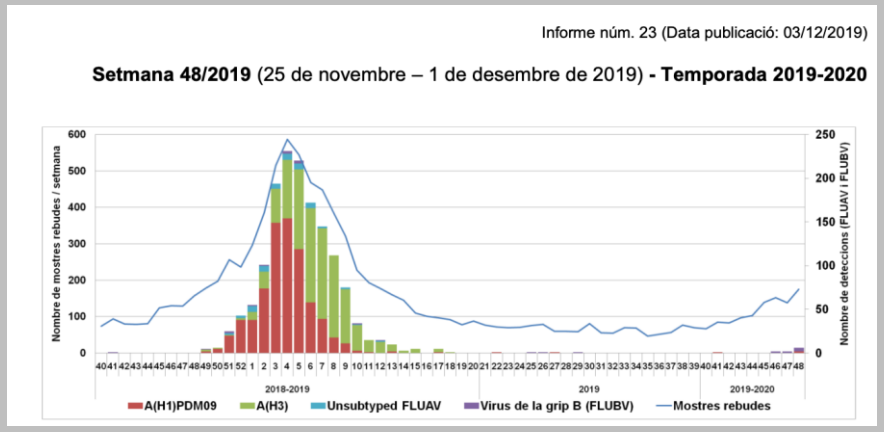
- **Surveillance. Real time information.**

- It is well known that children in their first years of life spread influenza in the community. Some of the influenza POC diagnostic systems have the capability of transmitting via cloud results in real time to a central laboratory, allowing a mapping of the positive cases, and enhancing virologic surveillance. This is a new approach that needs to be tested and it has to be analysed if it should be included in surveillance systems.

Benefits of Influenza POCT in paediatric primary care.

Surveillance. Real time information. Primary care and Reference Hospital. 2019-2020





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Final remarks. Take home messages.

- ✓ We have now adequate technology to be confident with Influenza POCTs in primary care. Old immunochromatographic tests should NOT be used. Only instrument based antigenic test (in children) or molecular tests (all ages) are adequate.
- ✓Price of the tests is an important issue in primary care.

- ✓ Tests have shown an **important decrease in the rate of additional visits in primary care**. There is a need to research this in different settings and health care systems.
- ✓ There is a **decrease in the use of antibiotics** although the extent of the difference is not yet clear and needs further research.

- ✓ The **use of high quality test s with adequate sensibility and sensitivity changes absolutely the management of the disease**. It allows clearer explanations to families and it enhances the confidence in the health care provider. An important value to be included in the cost benefit analysis.
- ✓ POCT used in paediatric primary care (0-6y) with a cloud system to provide data in real time to the reference laboratory can be useful for surveillance purposes.