Diagnostic dilemnas in respiratory viruses: point of care, multiple tests, targeted molecular tests

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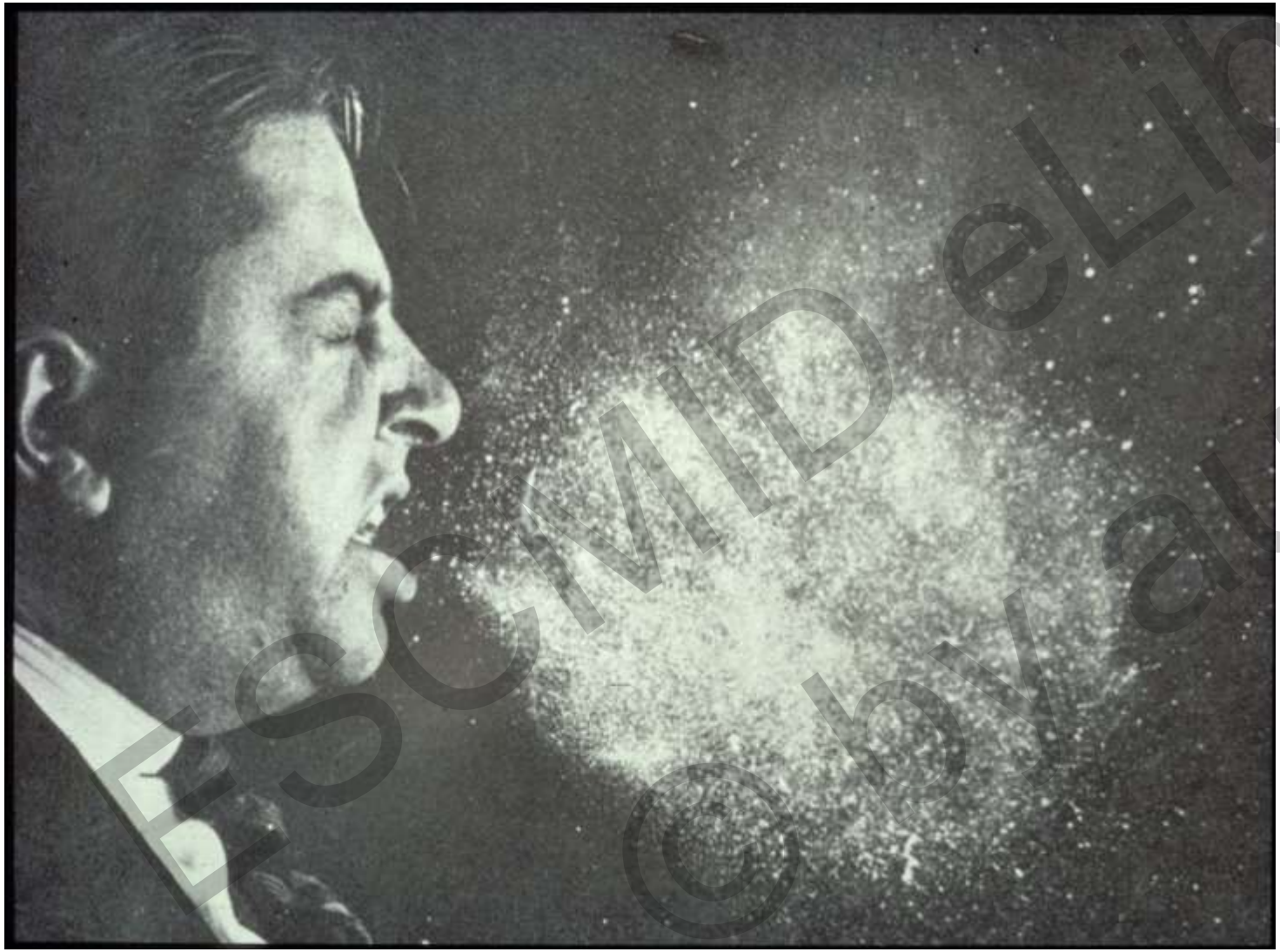
Disclosures

- Co Chair of Global Influenza Initiative
- Chair of Immuniser.Lyon
- Board member of GHISN foundation

- Travel and registration for Scientific meetings (Sanofi-Pasteur, GSK)

The lab dilemnas



What is the causative agent?

Was the sampling OK?
Have I the adapted technique and
Did I miss something (sensitivity)?

What were the symptoms?

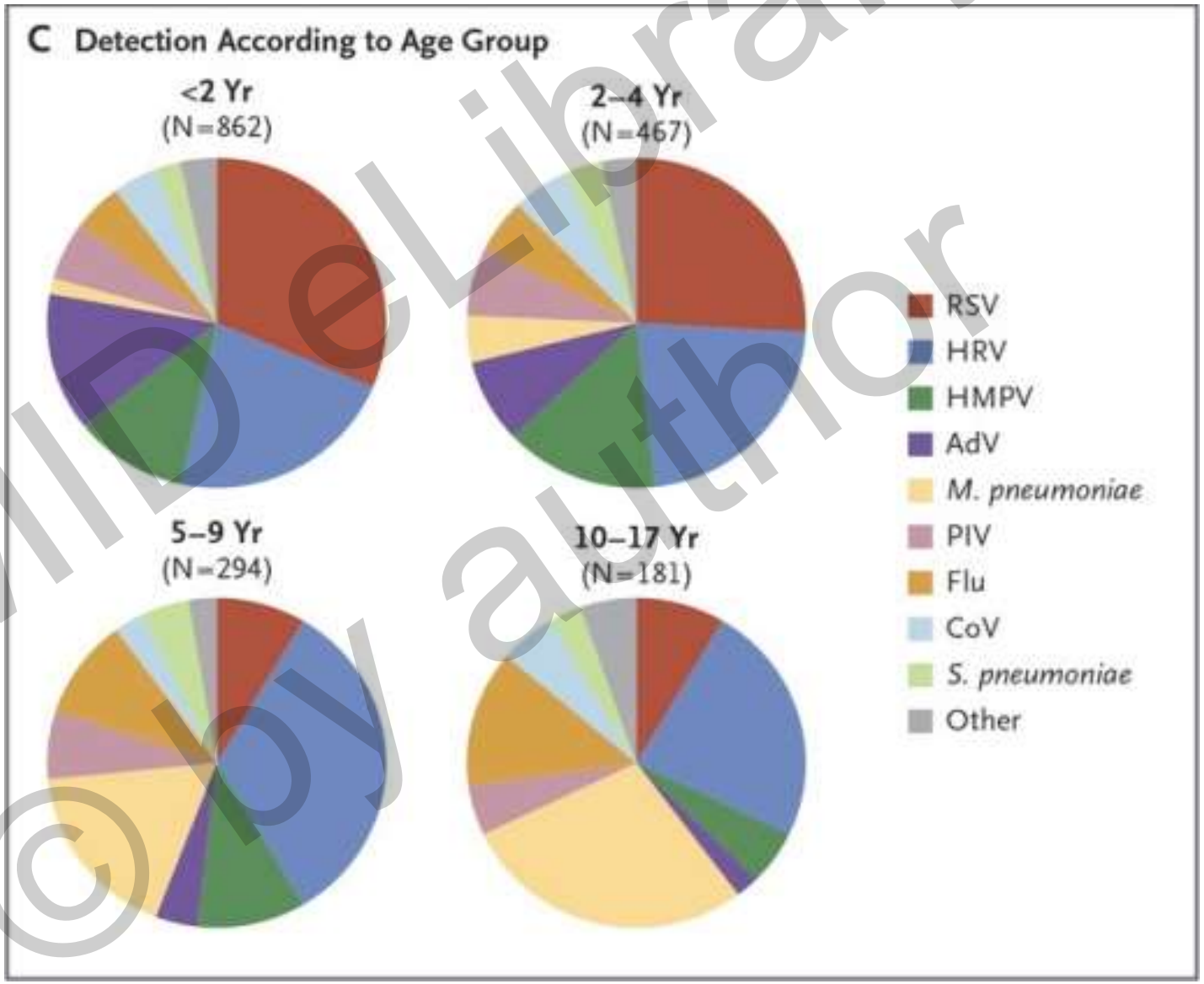
The clinician dilemnas

What is the causative agent?

Was the sample OK?
Have they the adapted technique and
Will they miss something (sensitivity)?

When will I get the answer?

Respiratory viruses, numerous aetiologies…



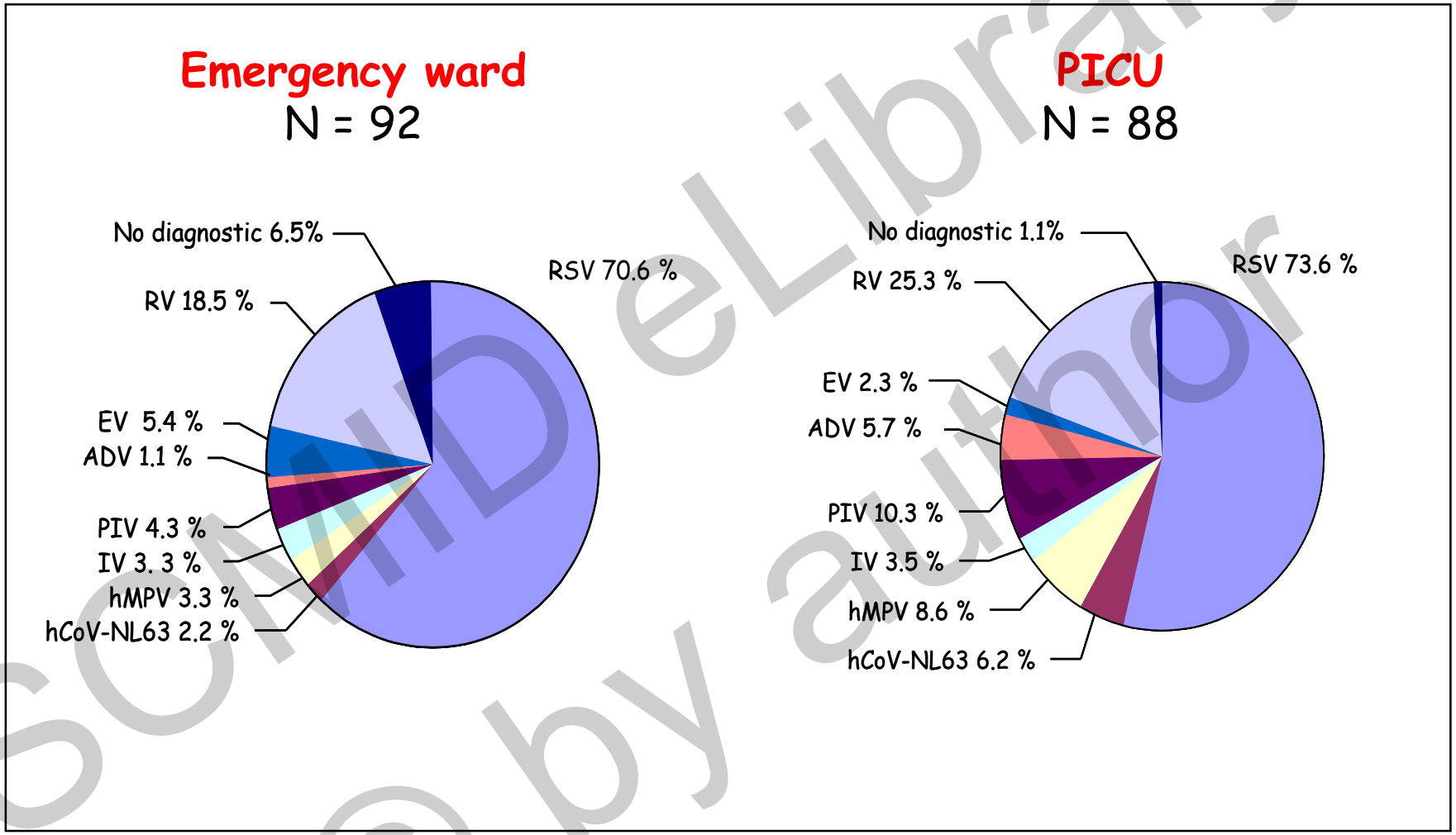
Jain S et al. N Engl J Med 2015;372:835-845.

Molecular diagnostic tools for respiratory viruses

- Molecular techniques have displaced the other techniques
  - Including potential alternative POC tools

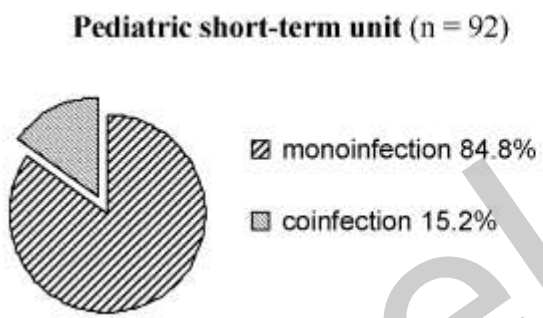
- Their added value and advantages are:
  - Their reliability
  - Their analytical performances
  - The rapidity (TAT)
  - Their adptability to the number of specimens to be analyzed
  - A trend toward user-friendly devices
  - High level of automation

It is possible to have a 100% diagnosis in clinical specimens



Richard N, et al Pediatr Infect Dis J. 2008 Mar;27(3):213-7,

It is possible to detect co-infections in clinical specimens



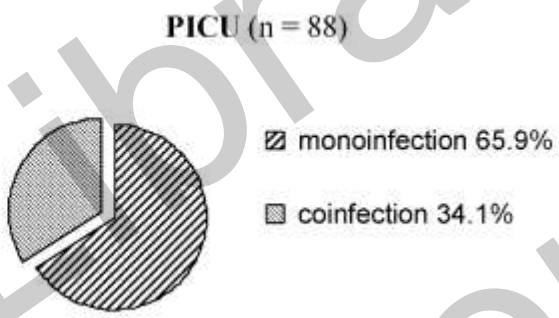


Table 2
Viral distribution in dual infection cases observed in pediatric intensive care unit (PICU) and pediatric short-term unit

Primary viral agent	Associated virus	Short-term unit (n = 14)	PICU (n = 30)
Respiratory syncytial virus	Rhinovirus	35.7	26.6
	hMPV	7.1	13.3
	hCoV-NL63	0	13.3
	Influenza A/B	14.3	6.6
	Parainfluenza virus	0	13.3
	Adenovirus	0	3.3
	Enterovirus	28.6	3.3
Rhinovirus	RSV	35.7	26.6
	hMPV	7.1	6.6
	hCoV-NL63	7.1	0
	Influenza A/B	0	0
	Parainfluenza virus	0	10
	Adenovirus	0	3.3
	Enterovirus	0	3.3
Parainfluenza virus	Influenza A/B	0	3.3

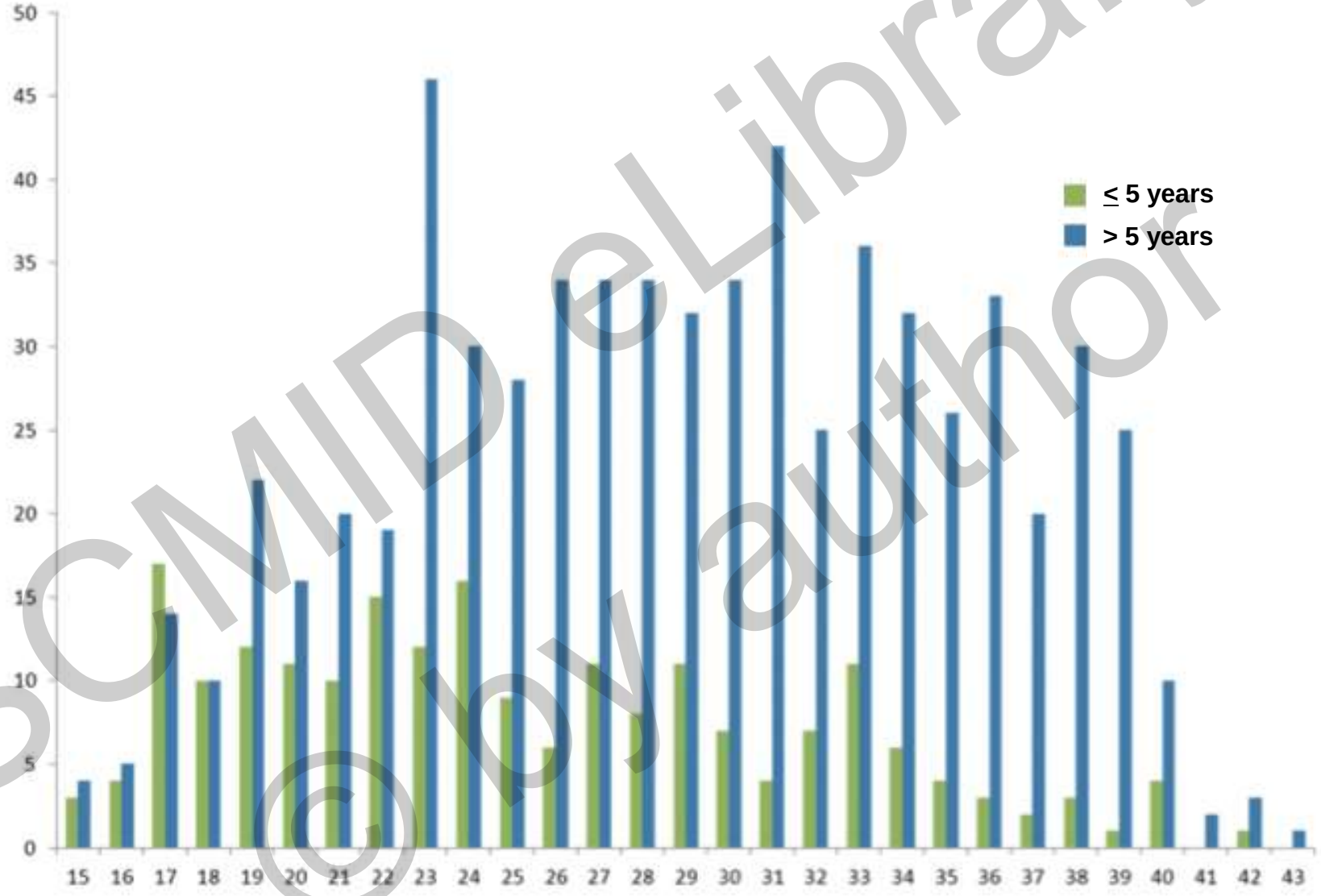
Data are presented as number of samples positive for dual infection (percentage of evaluated samples).

Richard N, et al Pediatr Infect Dis J. 2008 Mar;27(3):213-7,

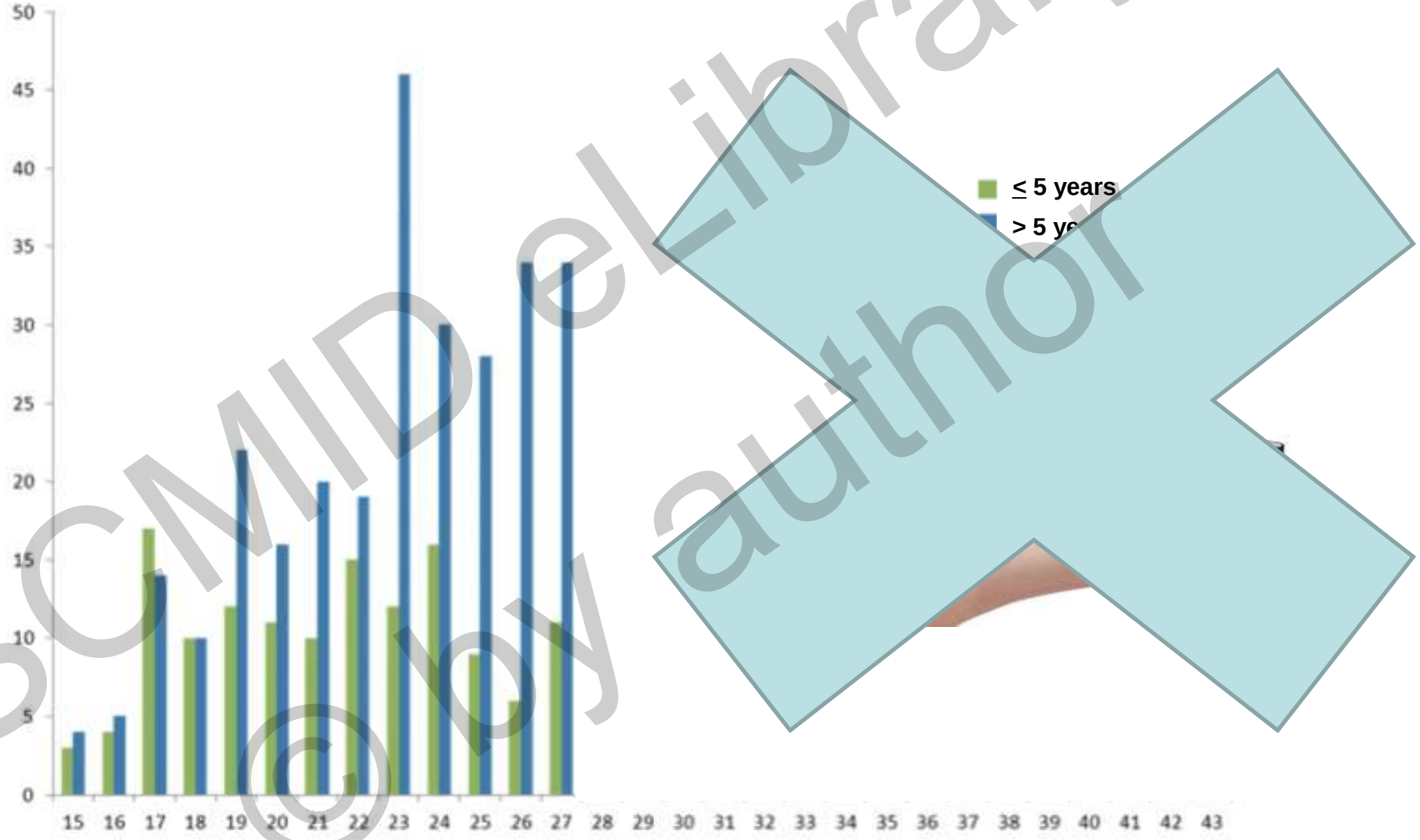
These questions have been asked for a long time

The landscape of molecular techniques

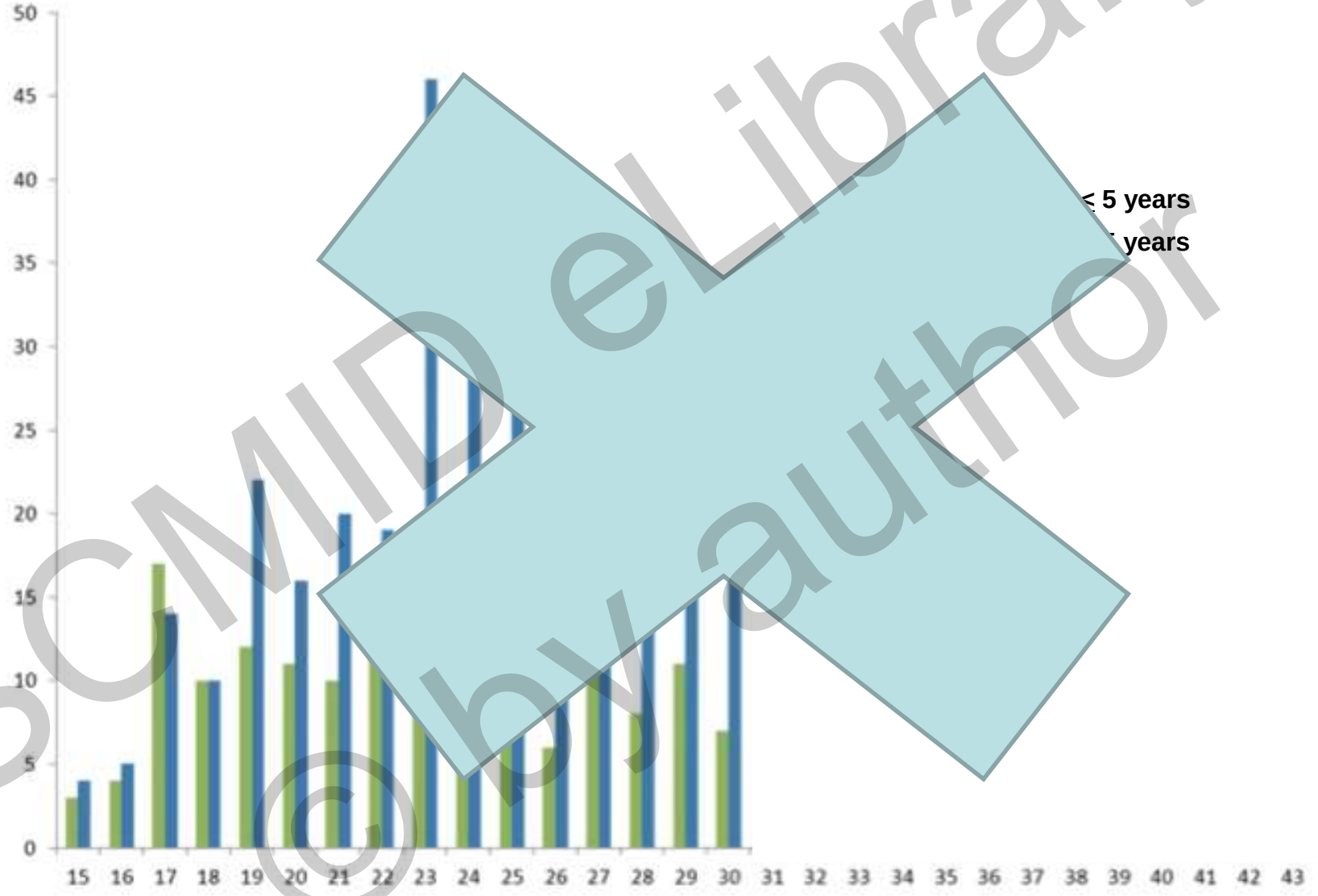
CT values from specimens collected in patients infected with influenza



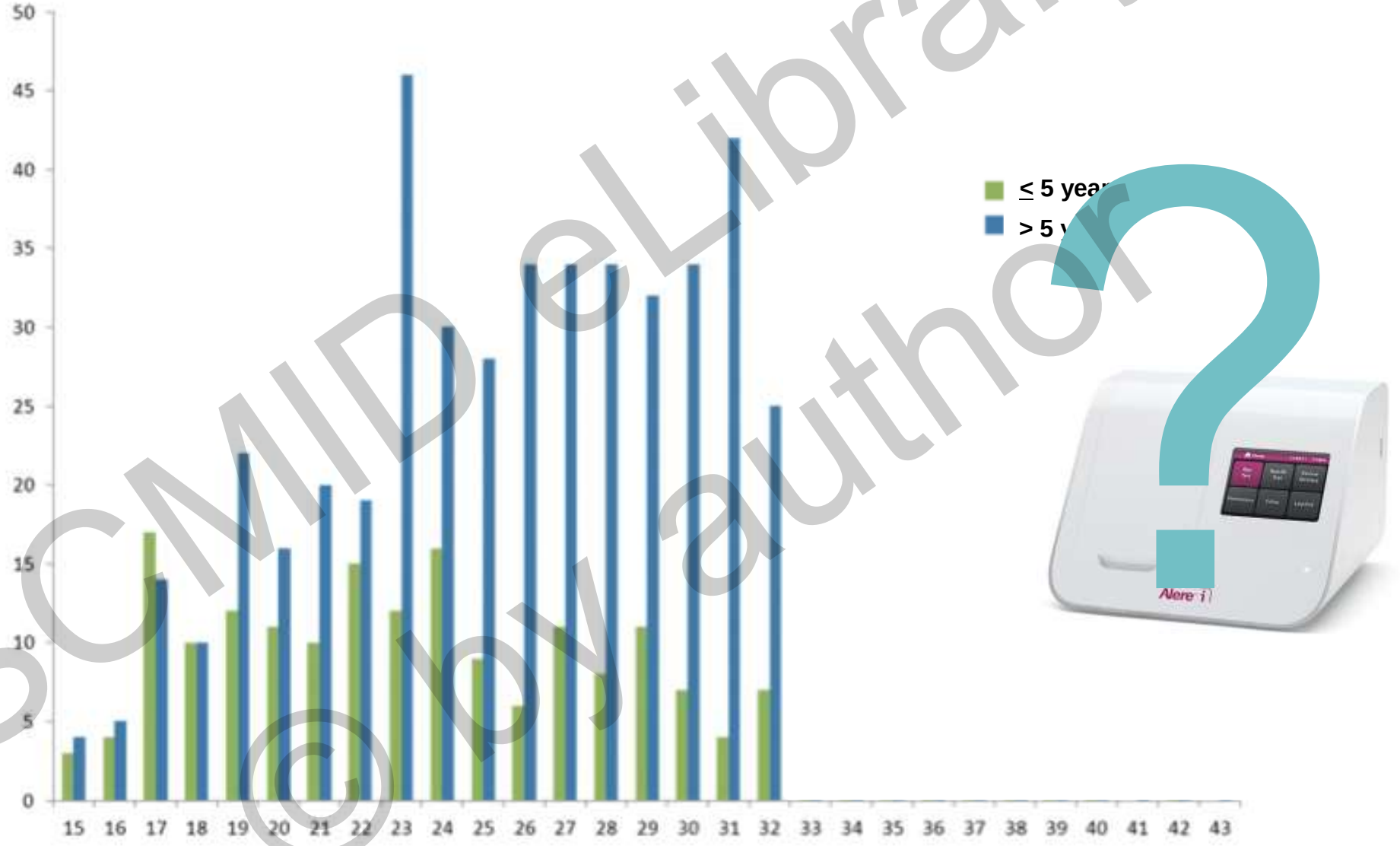
Sensitivity of detection for RIDT + reader



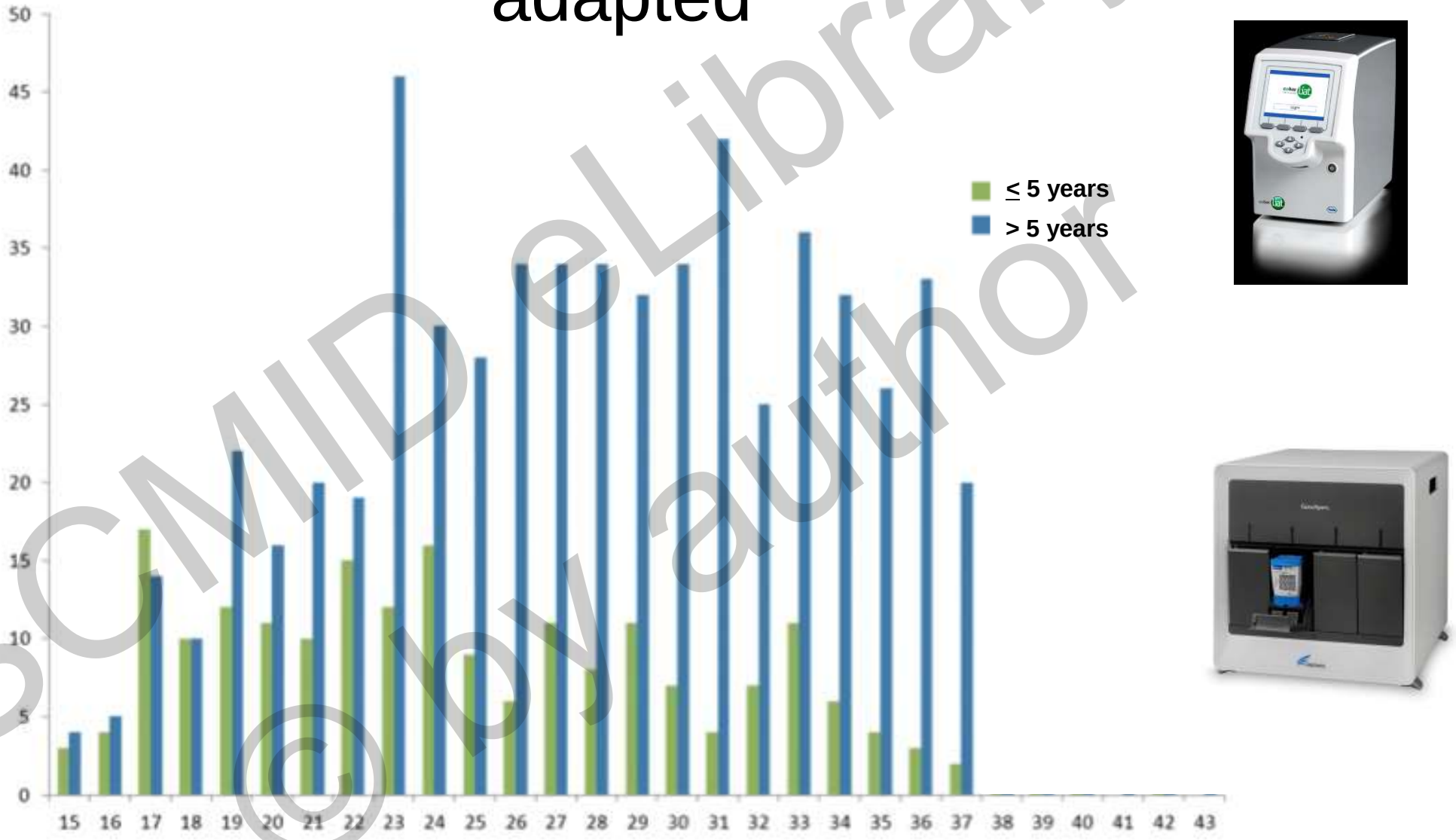
Sensitivity of detection for Virus isolation



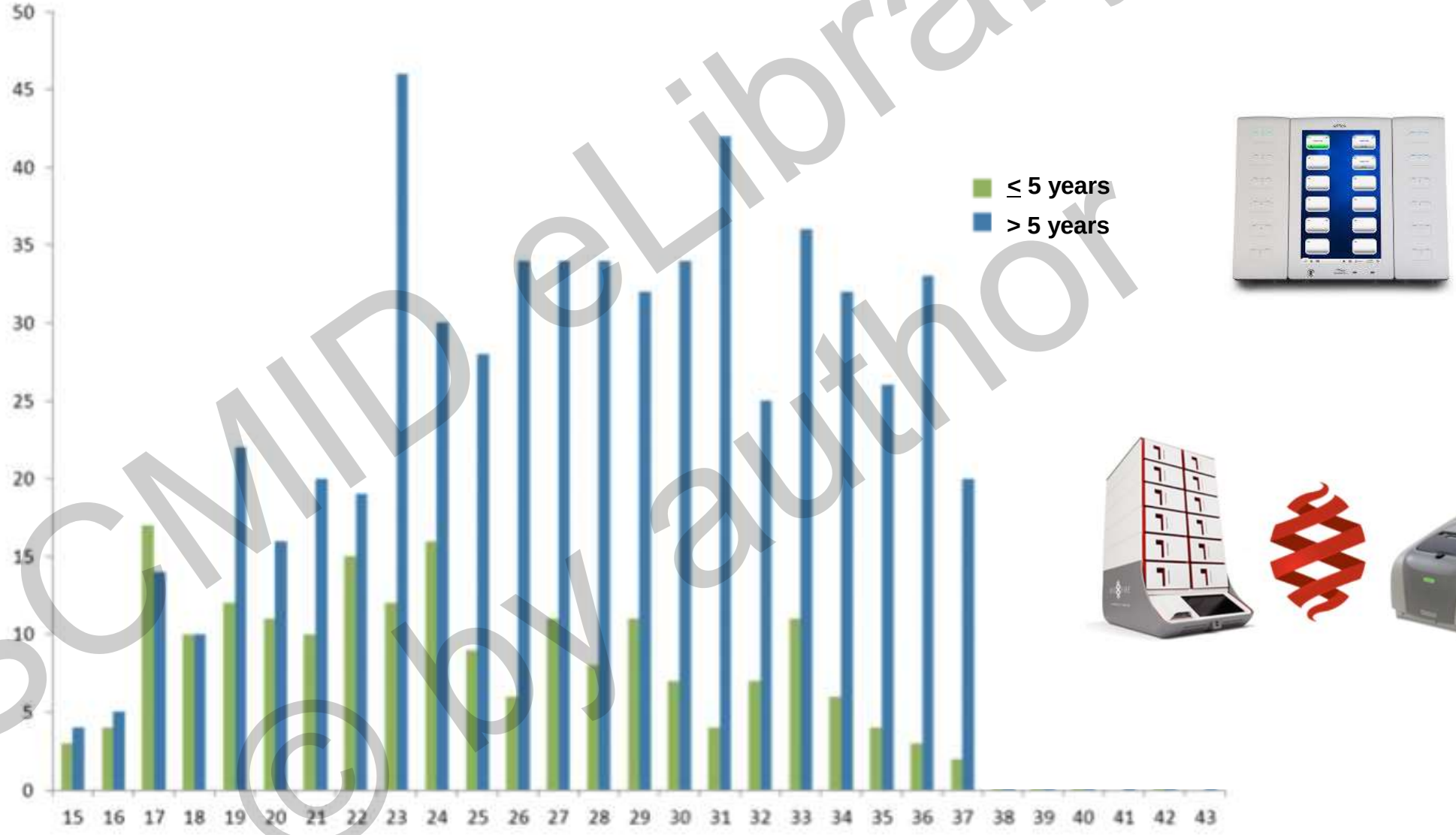
Sensitivity of detection for RIMD POC adapted



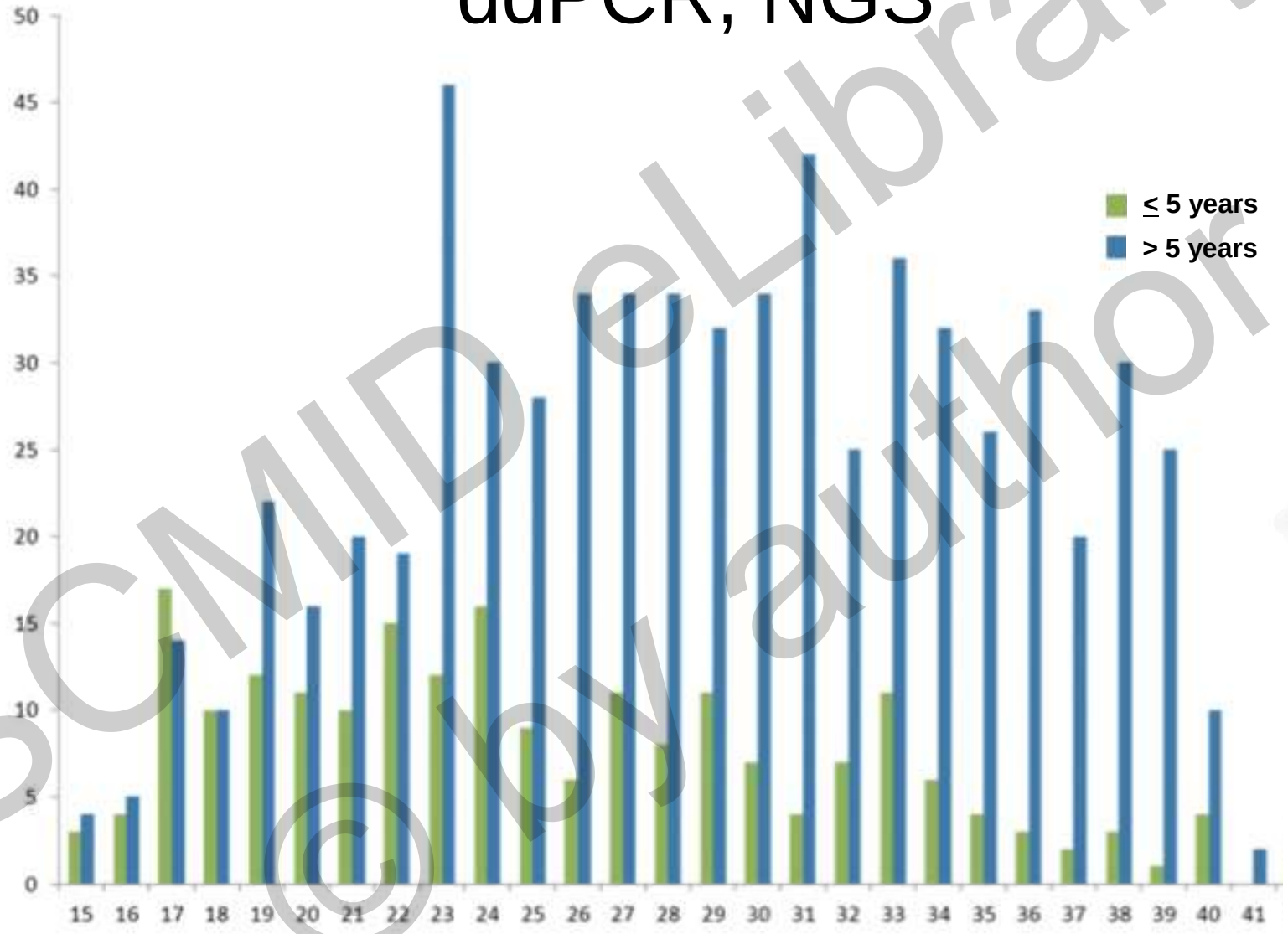
Sensitivity of detection for most of qRT-PCR POC adapted



Sensitivity of detection for most of syndromic RT-PCR



Sensitivity of detection for NIC qRT-PCR, ddPCR, NGS



What are the questions ?

- How to use POC-adapted devices
  - Seasonality?
  - In lab or in ward?
  - Is monoplex detection acceptable
  - How to detect the unexpected
  - Can it be bind to an algorythm

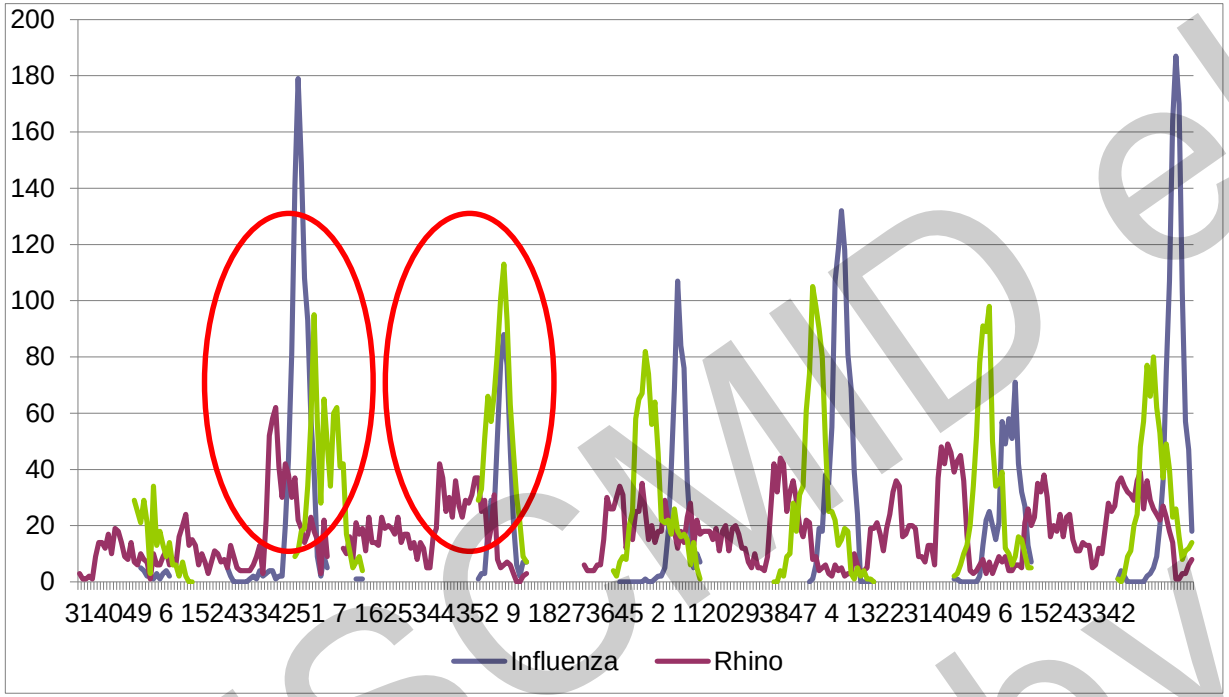
- How to use multiplex devices
  - Is the screening relevant in all cases
  - How to handle a large number of cases
  - How to interpret multiple detection (especially when no Ct values are provided)

- Are these approaches cost-effective

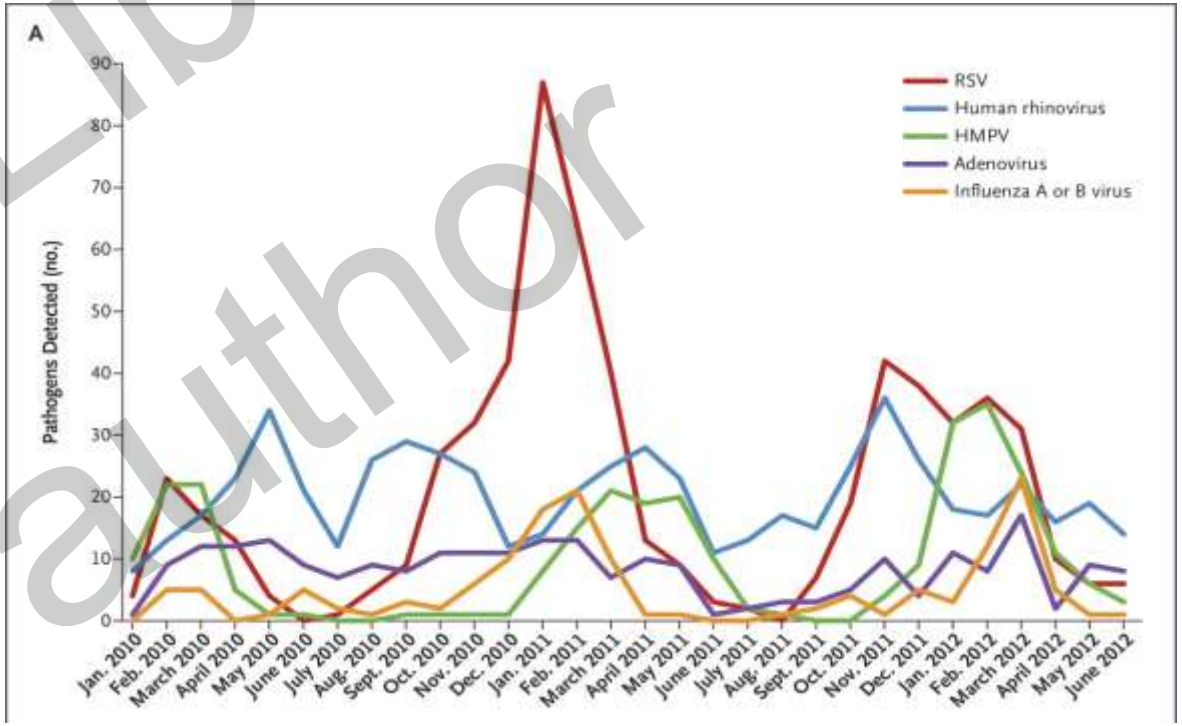
Fact # 1: Respiratory virus diversity

- Influenza A, B (& C)
- Respiratory Syncytial Virus (A & B)
- human Metapneumovirus (2 genogroups)
- Parainfluenzavirus (1, 2, 3 & 4)
- Adenovirus (8 genogroups, 60 serotypes)
- Rhinovirus (>150 serotypes)
- Enterovirus (>100 serotypes)
- Coronavirus (at least 6 serotypes)
- Bocavirus
- others…

Potential for co-circulation of viruses



Data from Lyon, France

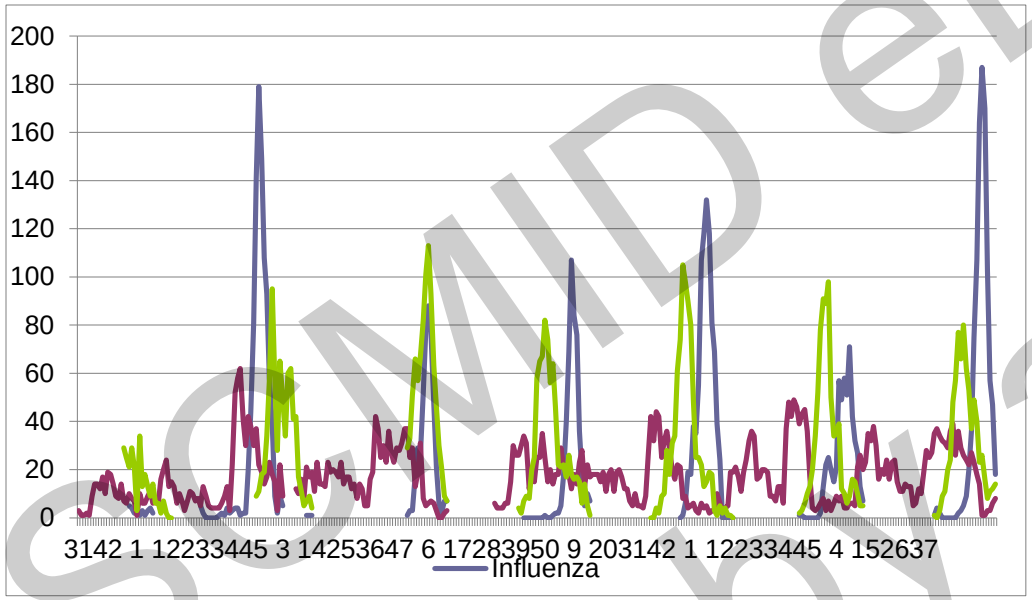


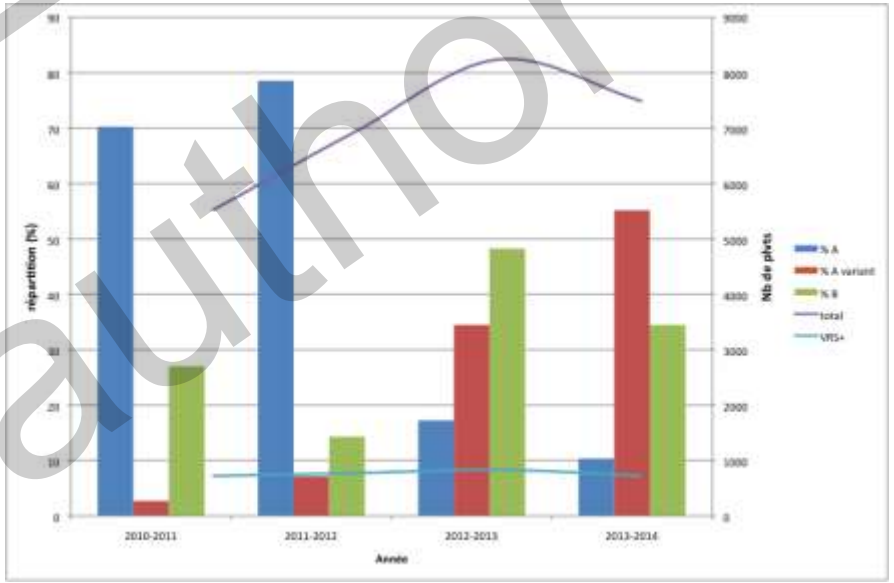
Jain S et al. N Engl J Med 2015;372:835-845.

Fact # 2: we have tpo keep in mmind the search for pathogenesis and unexpected viruses

- Influenza A, B
  - Antigenic variants
  - Resistance to antivirals
- Respiratory Syncytial Virus (A & B)
  - Emergence of evolutive mutants
- Enterovirus (>100 serotypes)
  - Emerging EV68 out of regular panels
- Coronavirus
  - Imported cases must not be missed
- Others…

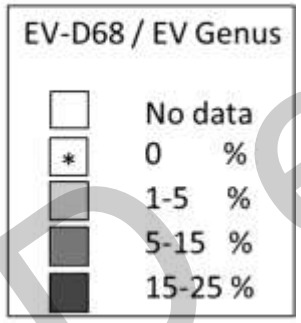
More cases of RSV due to the Emergence of the novel RSV-A ON1 genotype

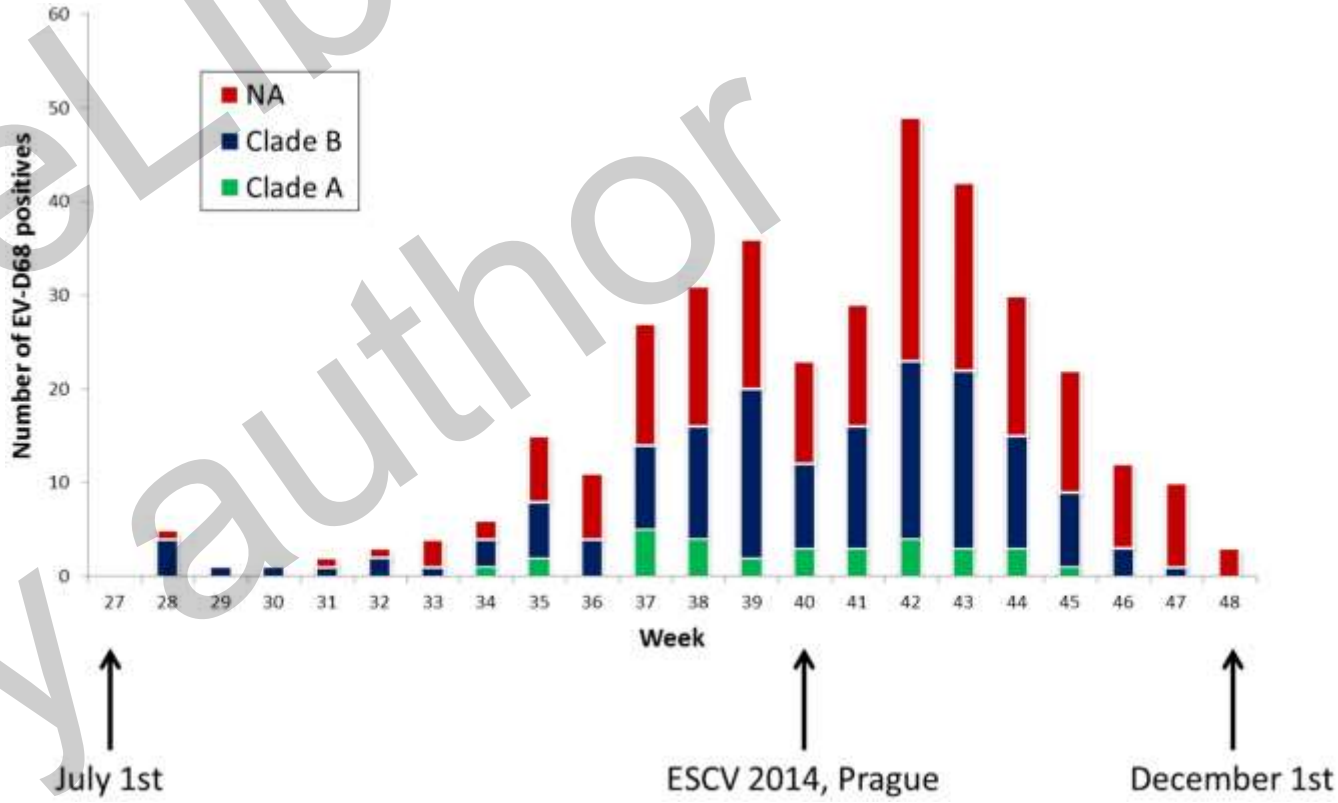




Bouscambert et al, in press, Eshaghi et al, Plos One 2012

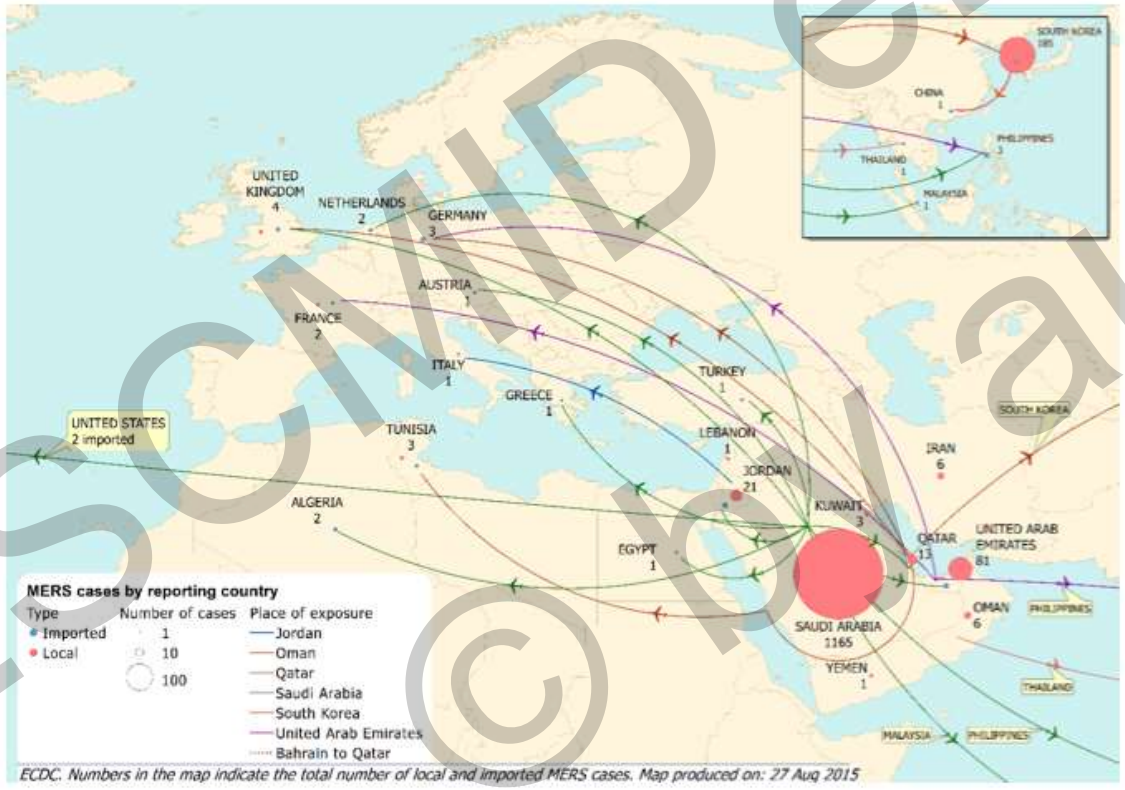
ESCV tribute to new emerging viruses : emerging EVD-68 in 2014

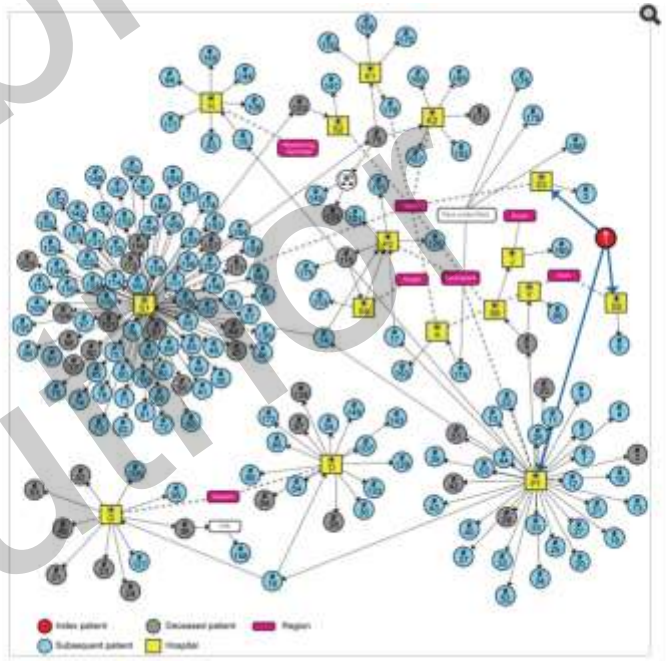




Poelman et al, JCV 2015

Emerging MERS CoV:
The imported cases and the Korean cluster

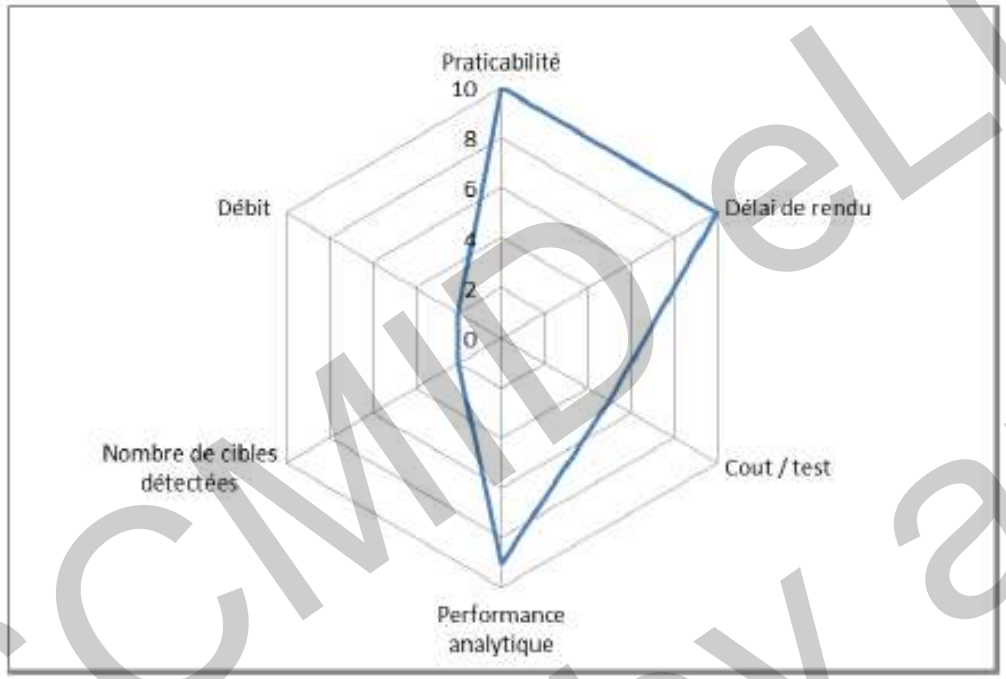




Choi J. Yonsei Med J. 2015

A bit of disease management and evaluation…

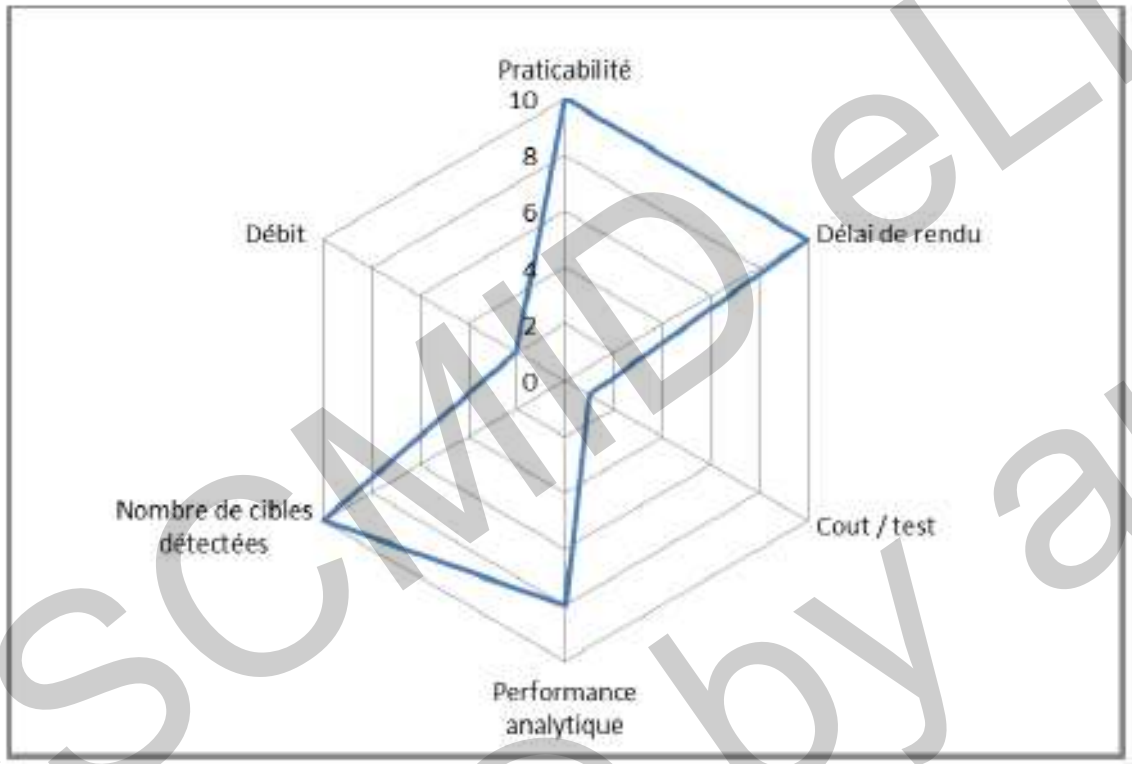
Evaluation of the rapid monoplex devices adapted for POC



Alere™ i (PCR)

GeneXpert ™ - Cepheid® (PCR)

Evaluation of the impact of the Multiplex assays



FilmArray®
bioMérieux®

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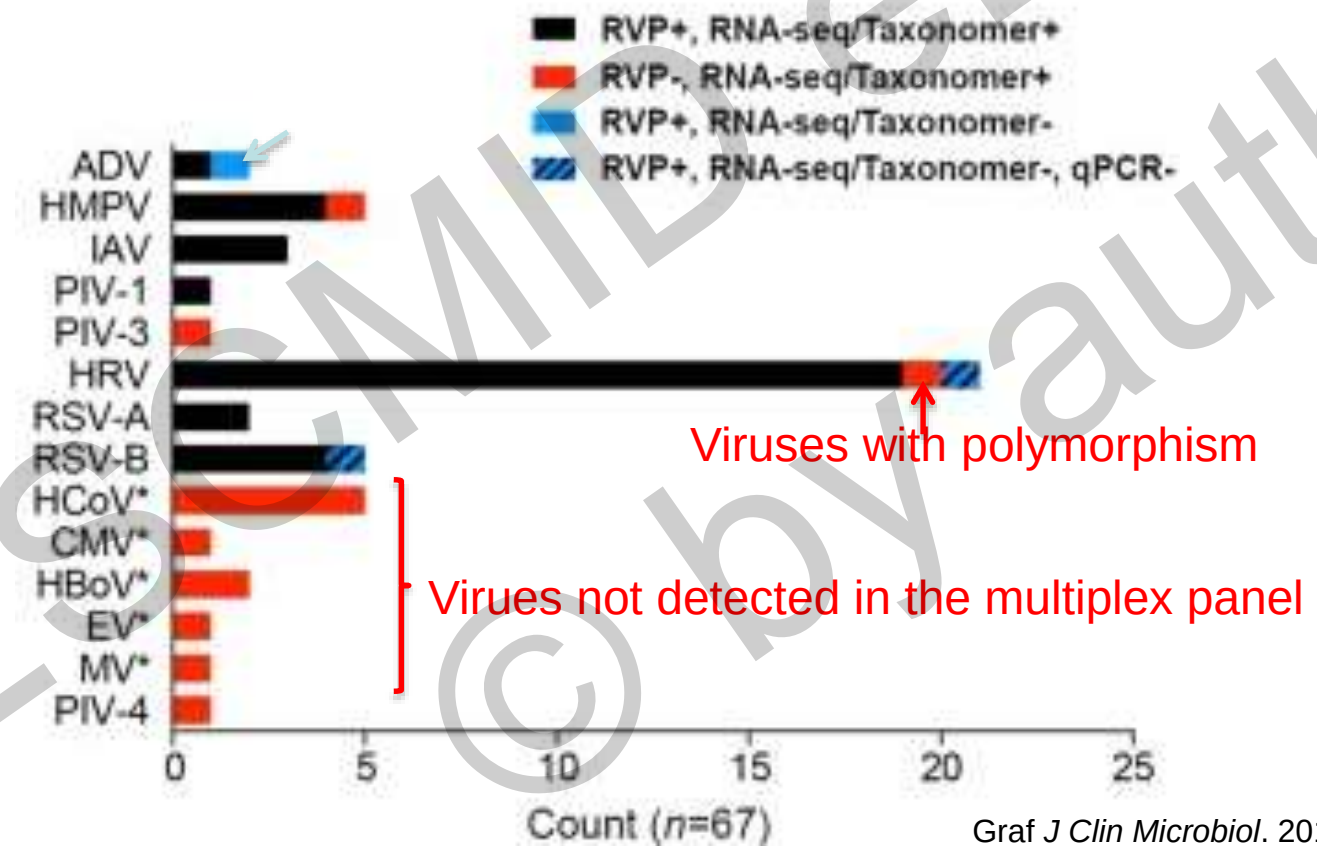
GenMark®

Preliminary data about their added value

- Ongoing cost effectiveness studies in Europe and in the USA will provide robust data about their added value
  - For POC devices
  - For multiplex devices
- Optimal use of these diagnostic tools will result in a better disease management
- These efficient molecular tools have both a good PPV and NPV, can be improved, and should be part of the diagnostic landscape
- Specific settings with poor diagnostic capacities will benefit from the development of these diagnostic tools.

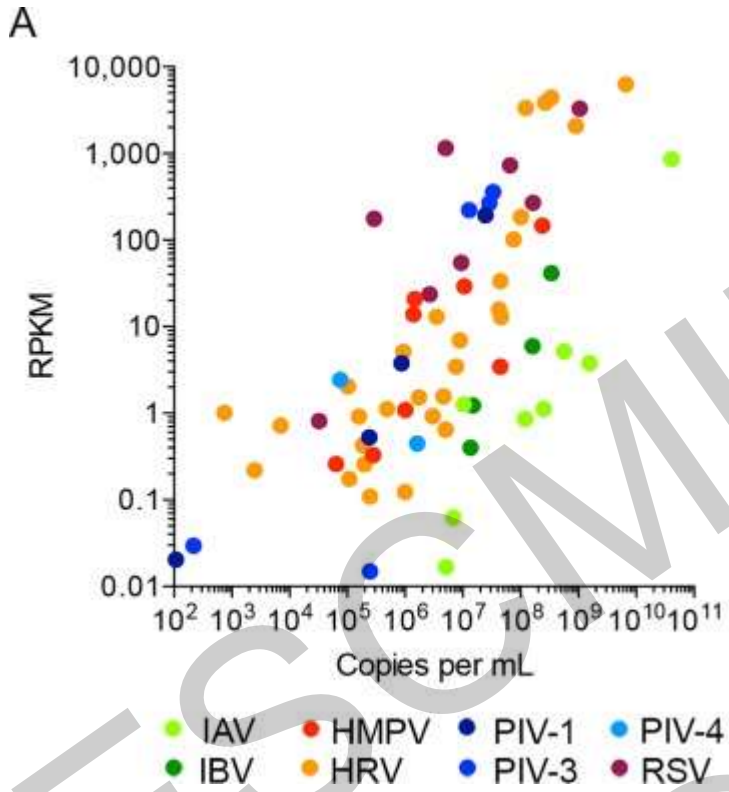
What is the next step?

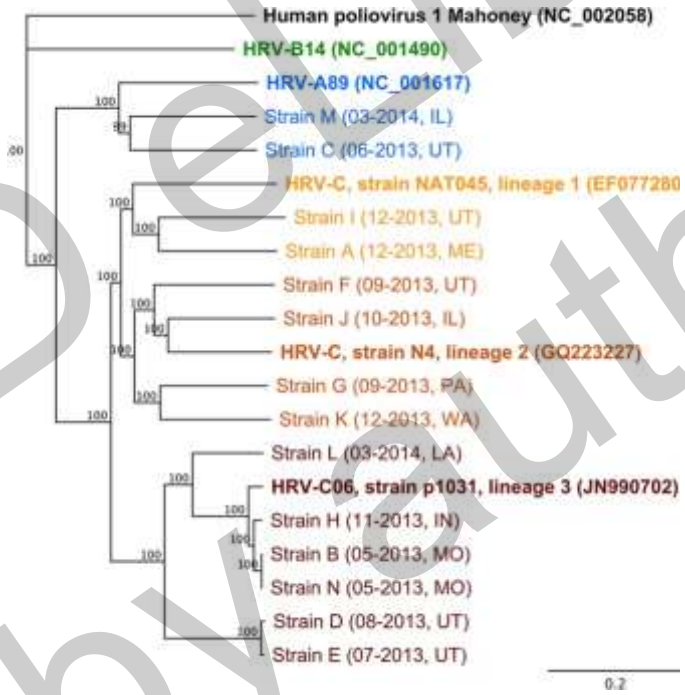
- NGS
  - Study on 67 NP swabs collected in <5 years-old children
  - RNA-seq vs syndromic PCR
  - Cofirmation of discrepant results by conventional PCR



Graf *J Clin Microbiol*. 2016

Additional added value of NGS





Graf *J Clin Microbiol*. 2016

Conclusions

Respiratory viruses are always bringing something new

The molecular tools can provide a diagnosis in 100% of the investigated cases, depending on the quality of the sample…

New molecular POC tools are user-friendly (kind of molecular diagnostic for the dumbs), rapid (short TAT), and ca provide real-time data that will be an added value for a better disease management. They tend to transfer the lab to the ward. These tests have their limits

New multiplex techniques are really powerfull, and should be used both for screening of complex cases. It will be an added value for a better disease management. They have their limits

This is not the end of the revolution, NGS will be the next step

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