Tackling COVID-19 through syndromic testing – QIAstat-Dx Respiratory SARS-CoV-2 Panel

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March 13, 2020

MAR 13 2020

QIAGEN gains BARDA funding for approval process of QIAstat-Dx test kit for SARS-CoV-2 coronavirus

- First syndromic testing solution to get U.S. agency's development support in novel coronavirus response
- QIAstat-Dx Respiratory SARS-CoV-2 Panel test kit will rapidly differentiate novel coronavirus from 21 other pathogens implicated in respiratory syndromes
- Further expanding QIAGEN's global mobilization to scale up testing supplies for the COVID-19 response

Hilden, Germany, and Germantown, Maryland, March 13, 2020 – QIAGEN (NYSE: QGEN; Frankfurt Prime Standard: QIA) today announced it will develop a new QIAstat-Dx test kit to differentiate the novel SARS-CoV-2 coronavirus from 21 other serious respiratory infections and will receive advanced development support from the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR). Accelerated development of the QIAstat-Dx test kit further expands QIAGEN's global mobilization for the emergency, which already includes a dramatic

March 18, 2020

MAR 18 2020

QIAGEN launches QIAstat-Dx test kit for detection of SARS-CoV-2 coronavirus in Europe following CE marking

- First syndromic testing solution to obtain CE marking as an in vitro diagnostic ("IVD") for the detection of SARS-CoV-2 , and is now available for purchase in the European Union
- QIAstat-Dx Respiratory SARS-CoV-2 Panel deployed in pandemic can differentiate novel coronavirus from 21 other serious respiratory infections with one sample and delivers results in about one hour
- Adds an important tool for clinicians as part of QIAGEN's global mobilization to scale up testing supplies for the COVID-19 response

Germantown, Maryland, and Hilden, Germany, March 18, 2020 – QIAGEN (NYSE: QGEN; Frankfurt Prime Standard: QIA) today announced that it has obtained CE marking for its newly developed QIAstat-Dx Respiratory SARS-CoV-2 Panel test to be sold as an in vitro diagnostic ("IVD") for the detection of SARS-CoV-2.

QIAGEN solutions at the forefront of SARS-CoV-2 testing

1. QIAstat-Dx Respiratory SARS-CoV-2 Panel
2. EZ1 RNA prep + Rotor-Gene Q analysis
3. QIAcube Connect RNA prep + Rotor-Gene Q analysis
4. Manual RNA prep + Rotor-Gene Q analysis

MAR 17 2020

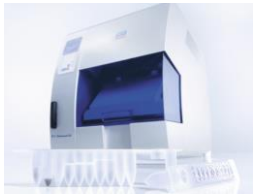
QIAGEN dramatically ramping up global production capacity for RNA extraction kits for use in detection of SARS-CoV-2 coronavirus

- Goal to reach global capacity for RNA nucleic extraction workflows for over 10 million patient tests a month by end of June 2020 and to reach capacity for 20 million monthly patient tests by end of 2020

QIAstat-Dx

QIAcube Connect

Rotor-Gene Q



EZ1 Advanced XL

- Supporting the global efforts has become our priority

Product availability varies by country specific regulatory requirements.

QIAstat-Dx Analyzer

Low maintenance requirements

Seamless integration with LIS connectivity

Intuitive interface and easy-to-use workflow

Up to 4 modules with GUI configuration

Ct values and amplification curves for each pathogen detected

Small footprint

Streamlined design with easy-to-read status indicator

Traceability controls using external and internal barcode readers

Benefits of the QIAstat-Dx cartridge solution

All-in-one mini-lab

- Convenient storage at room temperature
- Dry and wet reagents onboard

Easy sample input

- Liquid entrance
- Sample volumes 100µL - 500µL

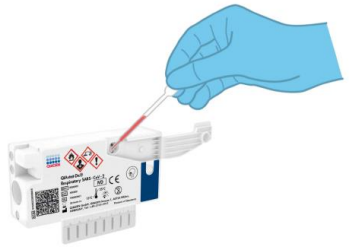
Reporting capabilities

- Detection up to 48 targets using real-time PCR
- Time to results – 1h

Efficient and fast operation to insert sample into QIAstat-Dx cartridge and start assay run

QIAstat-Dx – redefining ease of use

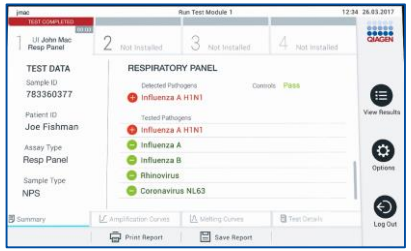
Transfer sample to main port of cartridge



Press the Run Test button and scan sample ID barcode

Scan barcode of cartridge to be used

Position cartridge on sample port – cartridge automatically moves in and test starts



Test results displayed

67 minutes

Ct value – where the value lies

- The Cycle Threshold Value (Ct value) is an indirect way of quantifying the concentration of the template relating it to the PCR cycle (time)
- Remove the “black box” – give laboratorians more information on every sample tested
- More information available when complex or unexpected results are received
- May provide information that indicates laboratory contamination

- Ct values and curves graphic information provided
- Color based positive pathogen differentiation
- Internal control (IC) specific Ct value
- Endpoint fluorescence value

QIAstat-Dx Respiratory SARS-CoV-2 Panel – dedicated reaction chamber

Use of the free 8th chamber of the QIAstat-Dx Respiratory Panel cartridge has enabled addition of SARS-CoV-2 targets without potential interference with existing targets

- When the QIAstat-Dx Respiratory Panel was developed, the 8th chamber was left empty as, at that time, the fluidics had not yet been tested
- In the QIAstat-Dx Respiratory SARS-CoV-2 Panel, primers and probes for the two SARS-CoV-2 targets are in the 8th chamber by themselves
- There can be no interference of the SARS-CoV-2 targets with detection of other targets in other reaction chambers
- Therefore, addition of SARS-CoV-2 targets does not compromise the validity of the QIAstat-Dx Respiratory SARS-CoV-2 Panel

QIAstat-Dx Respiratory SARS-CoV-2 Panel targets

19 Viral and 3 Bacterial Respiratory Pathogens

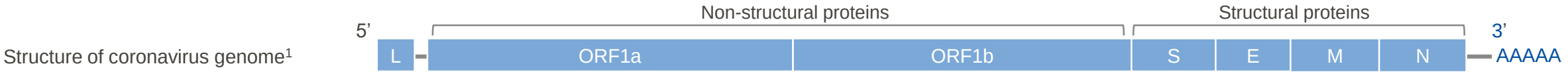
Pathogen	Classification (genome type)
Influenza A	Orthomyxovirus (RNA)
Influenza A, subtype H1N1/2009	Orthomyxovirus (RNA)
Influenza A subtype H1	Orthomyxovirus (RNA)
Influenza A subtype H3	Orthomyxovirus (RNA)
Influenza B	Orthomyxovirus (RNA)
Coronavirus 229E	Coronavirus (RNA)
Coronavirus HKU1	Coronavirus (RNA)
Coronavirus NL63	Coronavirus (RNA)
Coronavirus OC43	Coronavirus (RNA)
SARS-CoV-2	Coronavirus (RNA)
Parainfluenza Virus 1	Paramyxovirus (RNA)
Parainfluenza Virus 2	Paramyxovirus (RNA)
Parainfluenza Virus 3	Paramyxovirus (RNA)
Parainfluenza Virus 4	Paramyxovirus (RNA)
Respiratory Syncytial Virus A/B	Paramyxovirus (RNA)
Human Metapneumovirus A/B	Paramyxovirus (RNA)
Adenovirus	Adenovirus (DNA)
Bocavirus	Parvovirus (DNA)
Rhinovirus/Enterovirus	Picornavirus (RNA)
Mycoplasma pneumoniae	Bacterium (DNA)
Legionella pneumophila	Bacterium (DNA)
Bordetella pertussis	Bacterium (DNA)

Enterovirus and Rhinovirus are both detected, but not differentiated, with the QIAstat-Dx Respiratory SARS-CoV-2 Panel

QIAstat-Dx Respiratory SARS-CoV-2 Panel – SARS-CoV-2 targets

The SARS-CoV-2 targets in the QIAstat-Dx Respiratory SARS-CoV-2 Panel were designed using alignment of more than 186 publically available genomic sequences from the SARS-CoV-2 outbreak and are detected with one fluorophore

1. Orf1b gene (RNA-dependent RNA polymerase region) 2. E gene (envelope protein)



QIAstat-Dx Respiratory SARS-CoV-2 Panel	Orf1b	E gene	
Chinese National Institute for Viral Disease Control and prevention[2]	Orf1ab		N gene
US Centre for Disease Control and Prevention[3]			N gene 1 N gene 2 N gene 3
World Health Organisation[4]	Orf1ab	E gene	
Altona[5]		S gene E gene	
TIB Molbiol[6–8]	Orf1ab	E gene	N gene
Seegene Allplex 2019-nCoV[9]	Orf1ab	E gene	N gene

1. Zumla A, et al. Nat Rev Drug Discov 2016. 2. China National Institute for Viral Disease Control and Prevention 2020. 3. Centre for Disease Control and Prevention 2020. 4. World Health Organisation 2020. 5. Altona. RealStar Sars-CoV-R RT-PCR Kit Instructions for Use. 6. Roche. LightMix Modular SARS and Wuhan CoV E-gene. 7. Roche. LightMix Modular SARS and Wuhan CoV N-gene. 8. Roche. LightMix Modular Wuhan CoV RdRP-gene. 9. Seegene. Available at: http://www.seegene.com/assays/allplex_2019_ncov_assay

Sequence alignment

Genome analysis week 15: - 4404 SARS-CoV-2 genomes available

Panel	Assay	Number of genomes with non-critical single variations	Number of genomes with high risk single variations
WHO panel	E	16	1
	RdRp	14	0
	N	25	0
CDC (US) panel	N1	41	31
	N2	14	4
	N3	29	90
NMDC panel	RdRp	11	52
	N	17	610
HKU panel	RdRp	10	0
	N	25	1
QIAstat-Dx Respiratory SARS-CoV-2 Panel	RdRp E	11	7 *
TOTALS		213	796
ACUMMULATED TOTAL		1009	

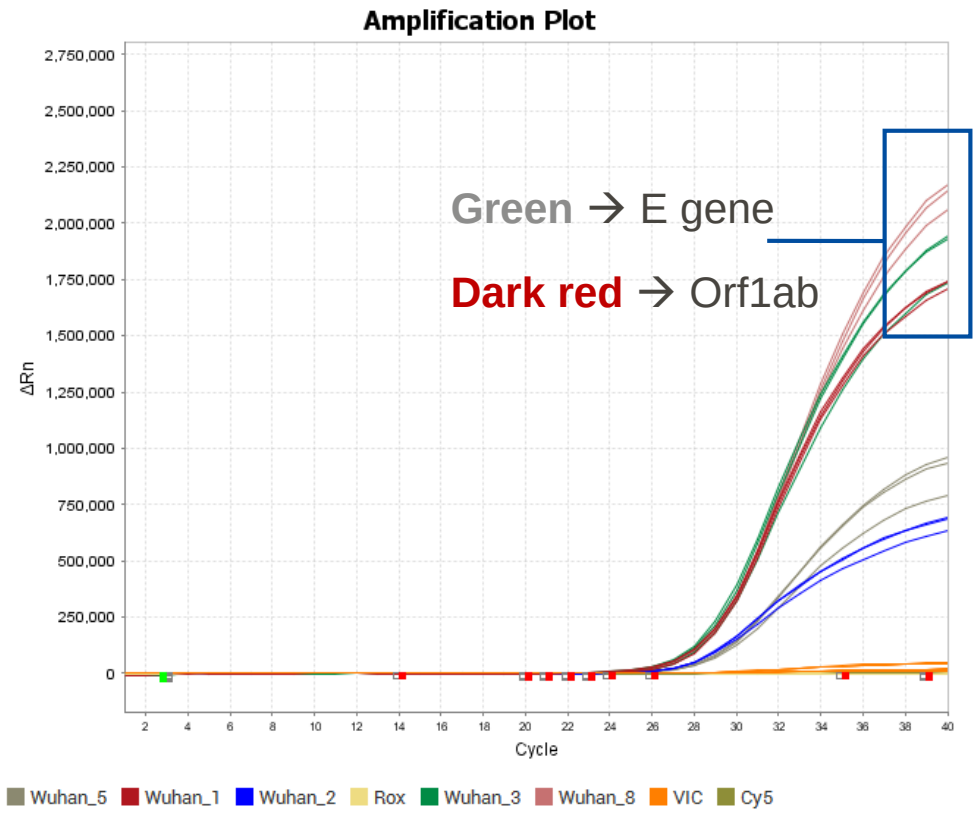
The 7 sequences contained the same potential high risk single nucleotide variant, and it has been tested in vitro (with a gBlock) .

- Sensitivity of the QIAstat-Dx Respiratory SARS-CoV-2 Panel assay remains unaffected.

Pennarubia L et al. *Manuscript under review IJID*

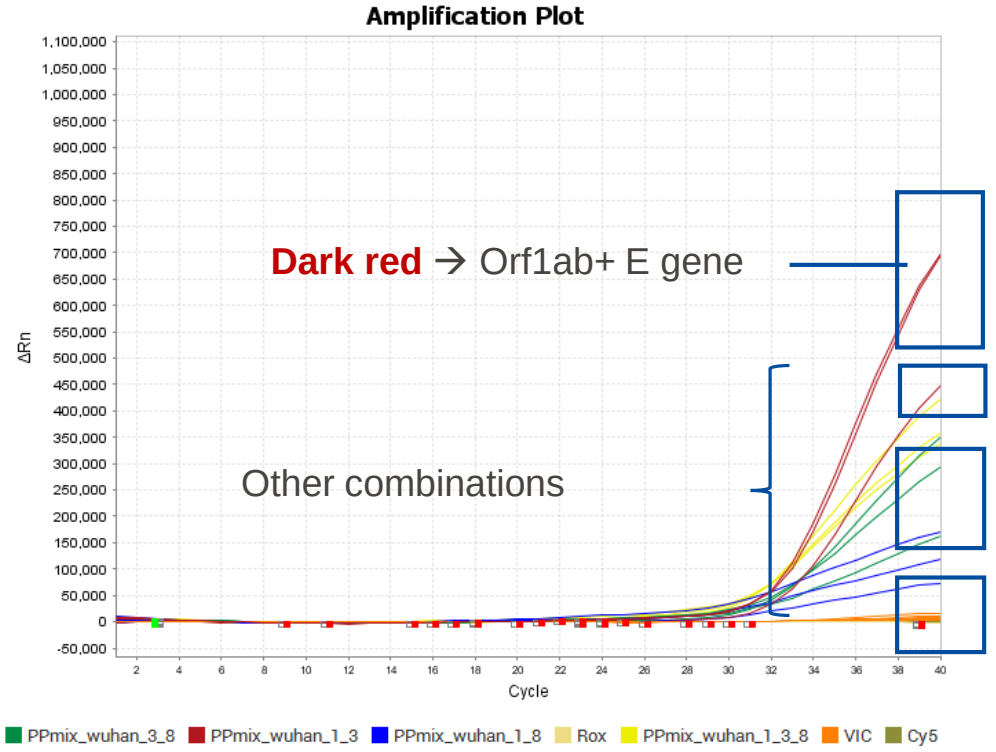
SARS-CoV-2 detection algorithm

Gene E and Gene Orf1ab (Rdrp) in singleplex



Gene E and Gene Orf1ab in multiplex ➔

The best performance for all the combinations tested



- 2 assays targeting different regions in the genome for additive sensitivity and best specificity.

QIAstat-Dx Respiratory SARS-CoV-2 Panel initial data and utility – CE-IVD

The QIAstat-Dx Respiratory SARS-CoV-2 Panel has been tested in a reference hospital in France

Validation data to be published soon

- Analytical sensitivity of the QIAstat-Dx Respiratory SARS-CoV-2 Panel is comparable to the WHO-Charité (Corman, et al)[1] method using serial dilutions of a clinical sample (Table right)
- No cross-reactions *in silico* vs other human pathogens or *in vitro* vs any other hCoV (HKU1, NL63, OC43, 229E, MERS, SARS) or other organisms observed in the QIAstat-Dx Respiratory Panel
- Comparison of bronchoalveolar lavage and tracheal aspirates (OFF-LABEL) showed equivalent level of sensitivity

NP swab samples (N=16)		WHO-Charité workflow	
		Positive	Negative
QIAstat-Dx Respiratory SARS-CoV-2	Positive	11	0
	Negative	0	5
		PPA: 100%	NPA: 100%

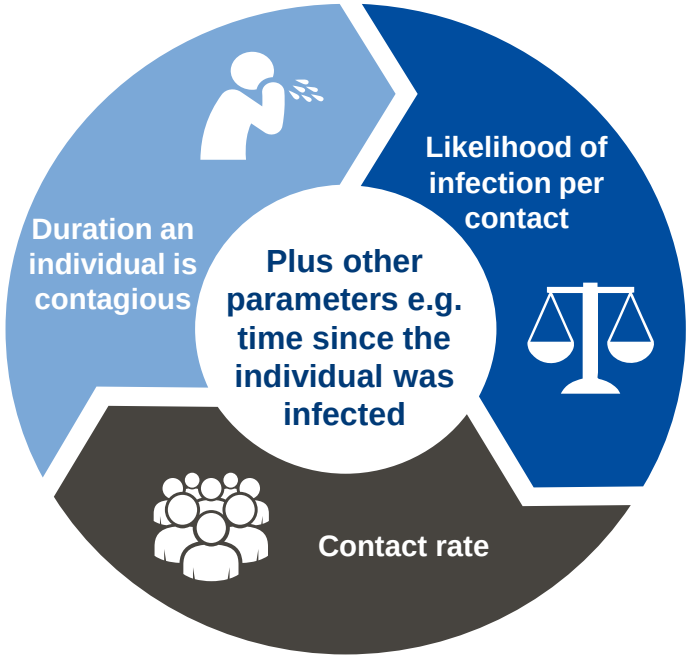
Data on file; Corman VM, et al. Euro Surveill 2020

SARS-CoV-2 pandemic – importance of time to diagnosis

Rapid diagnostics enable faster response times (e.g. isolation), limiting the spread of the infection

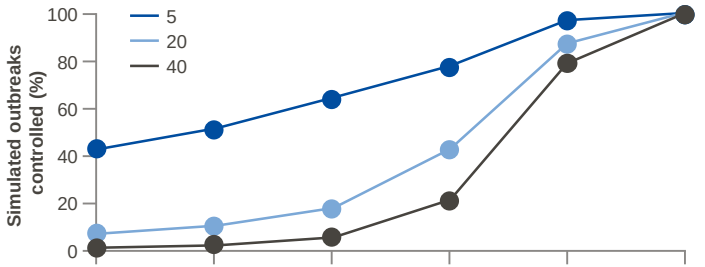
Syndromic testing enhances this response by discriminating between infections that cause similar symptoms
This can potentially free up resources (e.g. hospital capacity) for more severe infections

Pathogen transmission rate is influenced by[1]

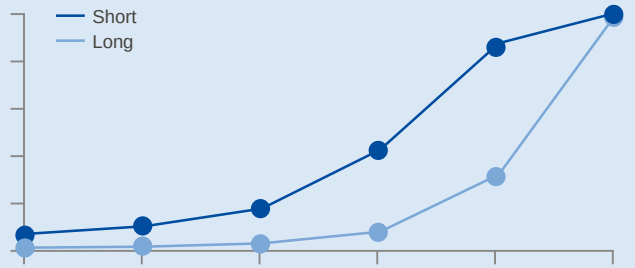


Shorter delays from symptom onset to isolation improves control* of outbreaks2

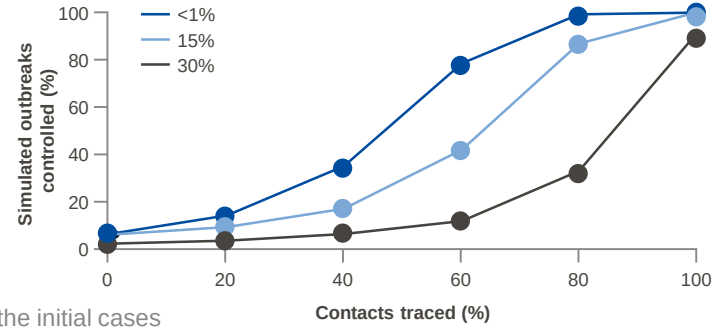
Initial number of cases



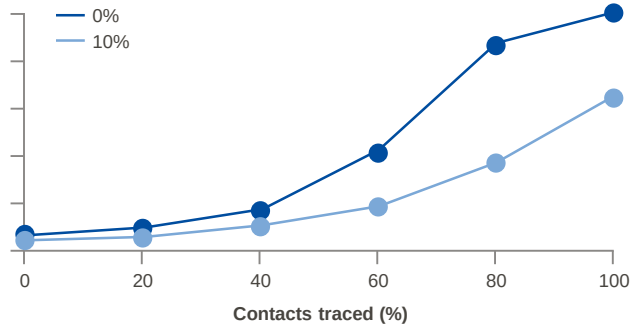
Onset to isolation delay



Transmission before symptoms



Subclinical infections



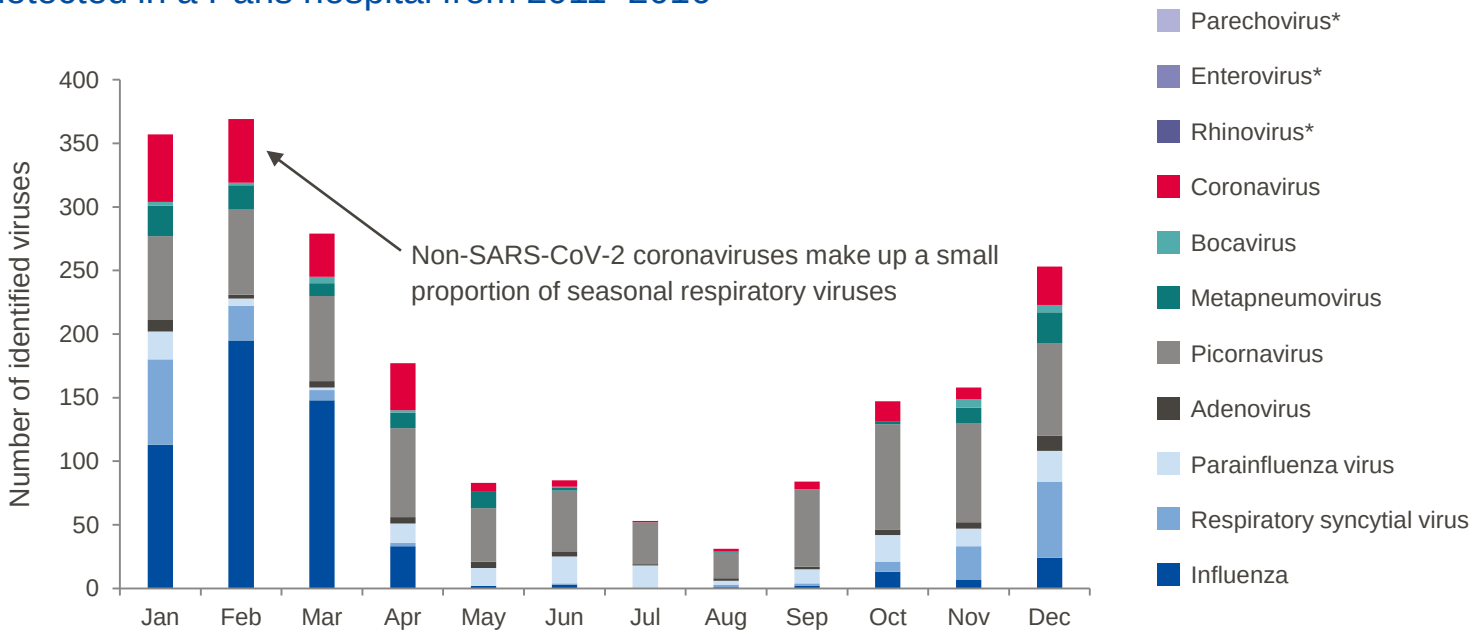
*Controlled simulated outbreak = no cases between weeks 12 and 16 after the initial cases
Figure adapted from Hellewell J, et al. *Lancet Glob Health* 2020; Fraser C, et al. *Proc Natl Acad Sci* USA 2004

SARS-CoV-2 diagnostics – importance of syndromic testing during COVID-19 pandemic

The wide variety of seasonal respiratory viruses creates a need for syndromic testing using a broad diagnostic panel of pathogens, particularly outside of the influenza season when the relative prevalence of non-influenza pathogens vs influenza virus greatly increases[1]

Syndromic testing is particularly valuable during the pandemic to distinguish SARS-CoV-2 from other causes of respiratory tract infection[2,3]

Monthly distribution of respiratory viruses detected in a Paris hospital from 2011–2016[1]

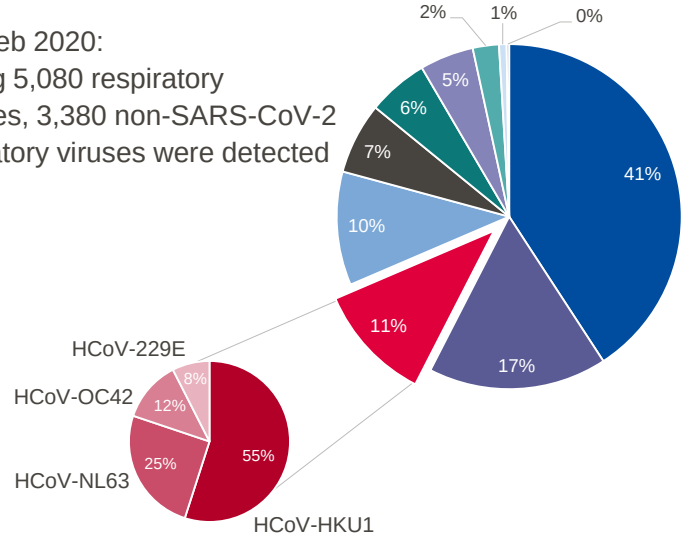


*Viruses not tested for in Visseaux, 2017

"Plenty of coronaviruses but no SARS-CoV-2" experience from a Marseille institute[2]

Up to 19 February 2020: 4,084 respiratory samples were tested for SARS-CoV-2 by PCR; **all were negative**

Jan–Feb 2020:
Among 5,080 respiratory samples, 3,380 non-SARS-CoV-2 respiratory viruses were detected



1. Visseaux B, et al. *PLoS ONE* 2017; 2. Colson P, et al. *Euro Surveill* 2020; 3. Reusken CB, et al. *Euro Surveill* 2020.

Syndromic testing in the context of COVID-19

Molecular assays for respiratory pathogens:

- QIAstat-Dx Respiratory Panel (differential diagnosis)
- WHO protocol for SARS-CoV-2 testing

		Patients with pathogen detected	
	Pathogens	n	%
Infections with a single pathogen	None	56	44.4
	SARS-CoV-2	3	2.4
	Influenza A(H1N1)pdm09	12	9.5
	Influenza A(H3N2)	11	8.7
	Influenza Aa	3	2.4
	Influenza B	10	7.9
	HRV/EV	9	7.1
	HMPV	3	2.4
	H-CoV 229 E	2	1.6
	H-CoV NL63	2	1.6
	H-CoV HKU1	2	1.6
	Mycoplasma pneumoniae	5	4
	Legionella pneumophila	1	0.8
Mixed infections	Influenza A(H3N2) + RSV A/B	2	1.6
	HRV/EV + RSV A/B	1	0.8
	HRV/EV + influenza B	1	0.8
	HMPV + adenovirus	1	0.8
	H-CoV 229E + influenza B	1	0.8

Author's conclusions:

Rapid syndromic diagnosis facilitates timely therapy decisions:

- SARS-CoV-2 public health measures / therapy
- Administration of targeted therapy (Influenza)
- Stewardship / Reduction of stay in the hospital

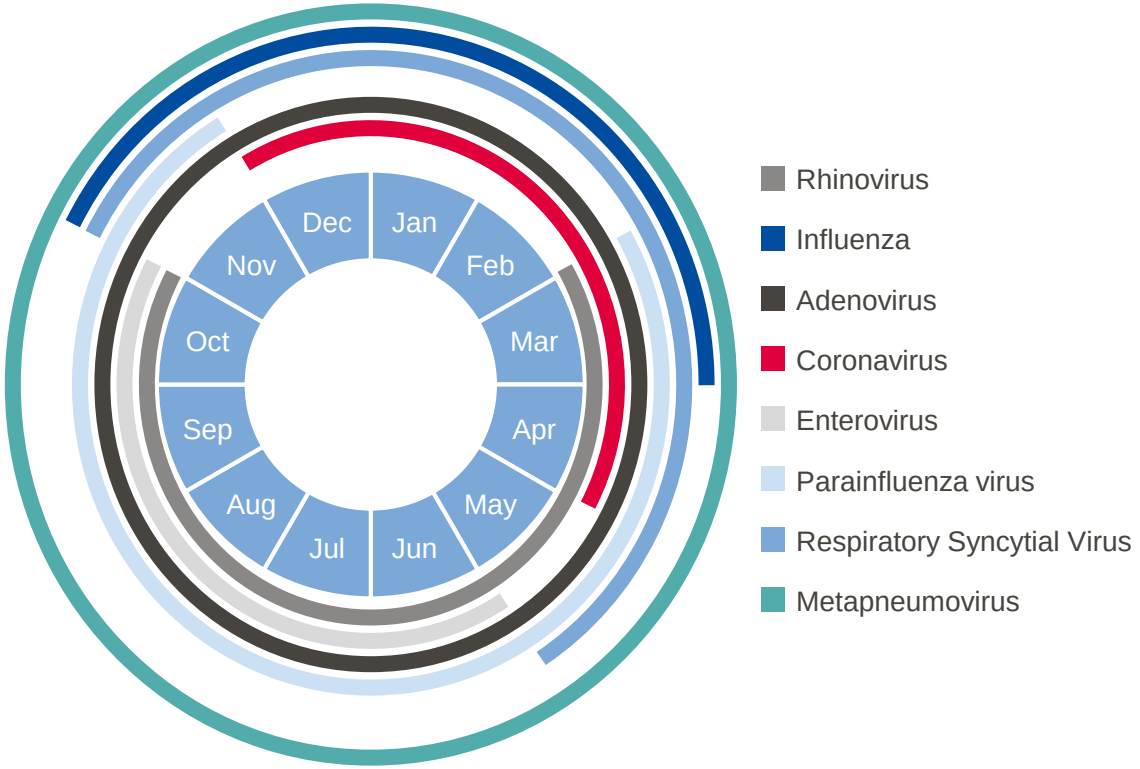
"Our results highlight the importance of using a syndromic molecular diagnostic panel for rapid detection of the most common respiratory pathogens, in order to improve evaluation and clinical management of patients with respiratory syndrome consistent with COVID-19. This is important in an epidemiological situation with low circulation of SARS-CoV-2, where alternative diagnoses may clarify an individual patient's risk and may allow adjusting public health containment measures"

Bordia L, et al. *Euro Surveill* 2020 Feb;25(8).

Could SARS-CoV-2 enter seasonal reoccurrence?

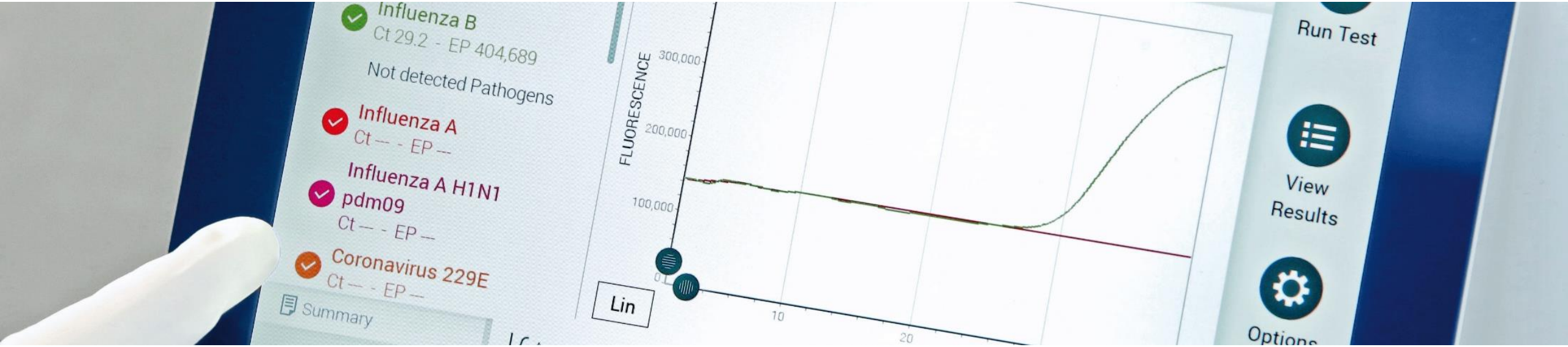
- Depends on seasonality, the duration of immunity, and the strength of cross-immunity to/from the other human coronaviruses[1]
- Modelling suggests that recurrent wintertime outbreaks of SARS-CoV-2 will probably occur after an initial pandemic wave[1]
- Longitudinal serological studies are urgently required to determine the duration of immunity to SARS-CoV-2, and epidemiological surveillance should be maintained in the coming years to anticipate the possibility of resurgence[1]

Seasonal variation of selected respiratory tract infection viruses[2]



In this scenario, syndromic testing is very important

1. Kissler et al, *Science* 10.1126/science.abb5793 2020; 2. Meneghetti, A. 2018 Medscape.



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The QIAstat-Dx Analyzer, the QIAstat-Dx Respiratory Panel and the QIAstat-Dx Respiratory SARS-CoV-2 Panel are intended for in vitro diagnostic use.