# Contribution of the laboratory in the fight against COVID-19: from the patient to public health perspective

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**1 March 2021**

# Olivier Vandenberg

- **Education**
  - Trained as Medical Doctor (ULB - 1996), Ms Laboratory Medicine (ULB, 2001), PhD thesis in Biomedical Sciences (ULB, 2006), PgDip Public Health (LSHTM, 2019)

- **Professional experience**
  - 2017- Head of the Innovation and Business Development Unit, LHUB-ULB, Brussels, Belgium
  - 2016- Honorary Senior Lecturer, Division of Infection & Immunity, University College of London, UK
  - 2016-17 Sabbatical leave: Division of Infection & Immunity, University College of London, UK
  - 2008 –17 Head of the Department of Microbiology, and Associated Director of LHUB-ULB, Belgium
  - 2008- Professor of Microbiology, Université Libre de Bruxelles (ULB), Belgium

    Environmental health and occupational health Research Centre, Public Health School, Université Libre de Bruxelles (ULB) Belgium
  - 2004 –15 Head of the Belgian National Reference Centre for *Campylobacter*

# Disclosures

- I have no personal or financial interests to declare.
- I have no financial support from an industry source for the current presentation
- I am member of several advisory boards of IVD's  manufacturers.
- The LHUB-ULB's Innovation and Business Development Unit strongly collaborates with  the industry to develop and/or improve new diagnostic solutions.
- The opinions expressed here are my own and not necessarily LHUB-ULB and/or ULB

# Presentation Outline

- Background
- Consideration about the laboratory diagnosis of SARS-CoV-2
  - Implementation of molecular diagnostic tests
  - Supply failure and PPE
  - Field collaboration with industrial/academic platforms and platforms bis
  - Reimbursement of testing
  - Development of alternative diagnostic methods
- Consideration on COVID-19 surveillance and public health strategy
  - Involvement of Laboratory Medicine Specialists in the decision process
  - Sentinel laboratory network
  - Sequencing platform
- Concluding remarks

# Laboratory Diagnosis of COVID-19 Infection: The LHUB-ULB's perspective

HUDERF

CHU Brugmann

CHU St-Pierre

Hôpital Erasme

Institut J. Bordet

Population density # hab. / km²

- < 5 000
- 5 000 - 8 000
- 8 000 - 14 000
- 14 000 - 18 000
- > 18 000
- < 20 habitants

Moyenne régionale : 7057,00

**"On time" quality result**
**Equality between sites in terms of service level**
**Fast and appropriate patient management**

N

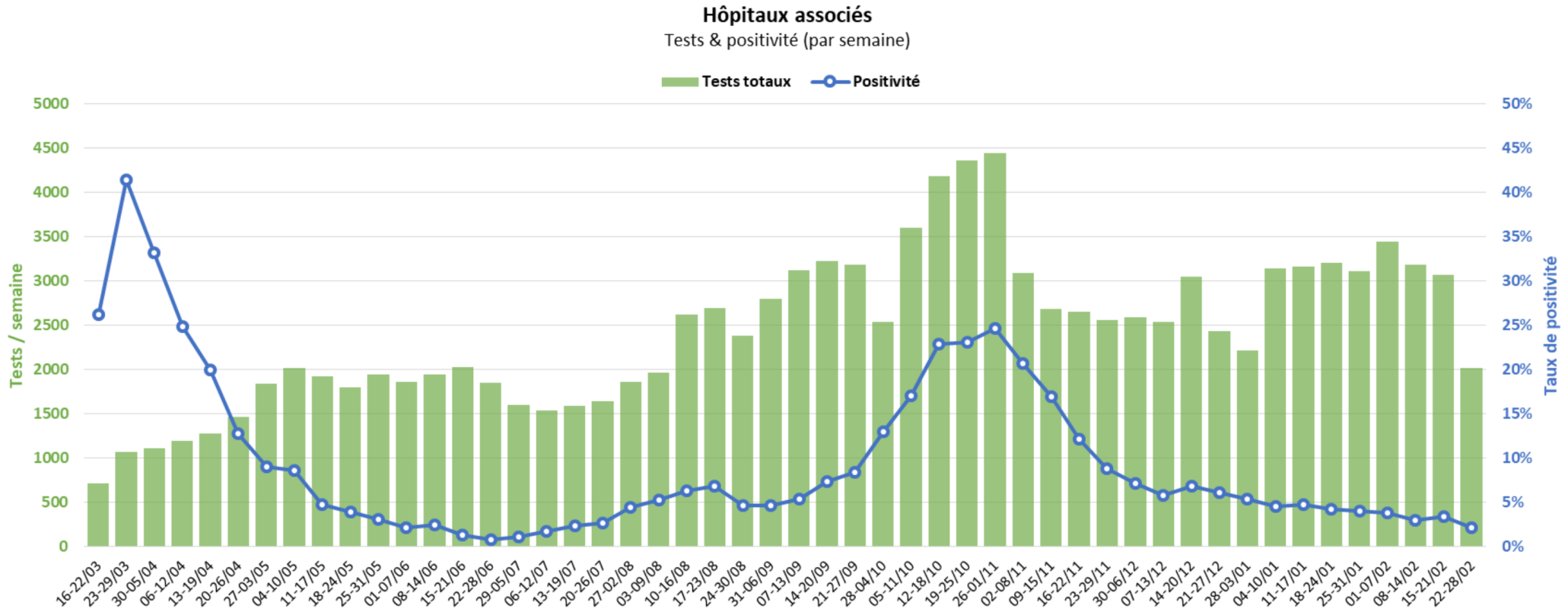
1 km
1 mi

*Source : IBSA, SPF Economie – Direction generale Statistique – Statistics Belgium. Monitoring des Quartiers – IBSA Brussels UrbIS*

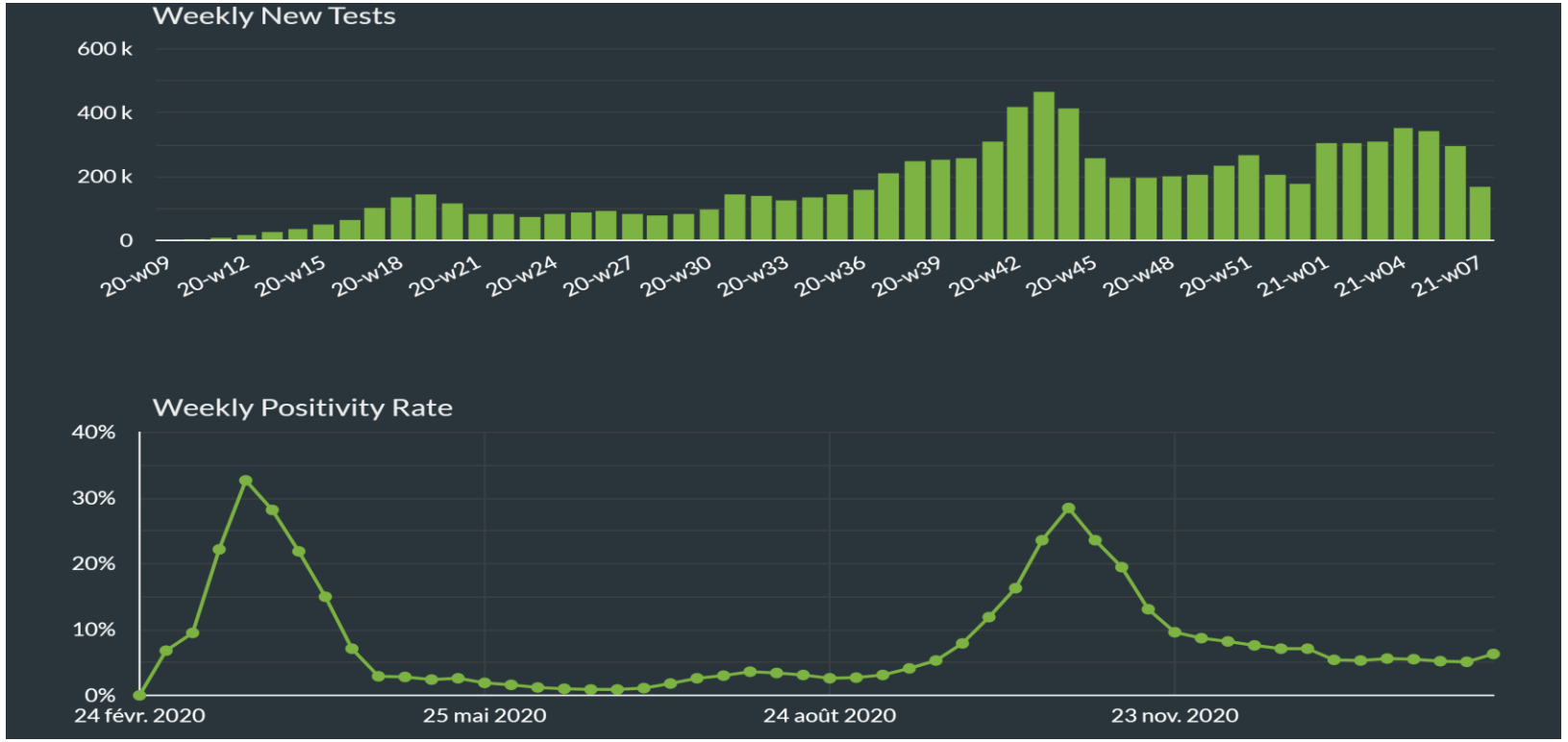
# The LHUB-ULB – Scope & Genesis

- The LHUB-ULB: Consolidated Clinical Lab structure/organization
- Our partners : 5 University Hospitals located in the Brussels Region on 9 sites – 2.903 beds – 3 primary geographical locations (Center, North, West)
  - Two large General Hospitals – Respectively 858 (Brugmann) & 626 (St-Pierre) beds
  - Two medium-size Specialty Hospitals (cancer, paediatrics) – Respectively 160 (I. Bordet) and 183 (HUDERF) beds
  - One large Academic Hospital (Erasme) – 1076 beds
- Analysis Volumes:
  - CHU St-Pierre + I. Jules Bordet : 6M/yr
  - CHU Brugmann + HUDERF : 6M/yr
  - Erasme : 6M/yr

# Laboratory Diagnosis of COVID-19 Infection: The LHUB-ULB's perspective



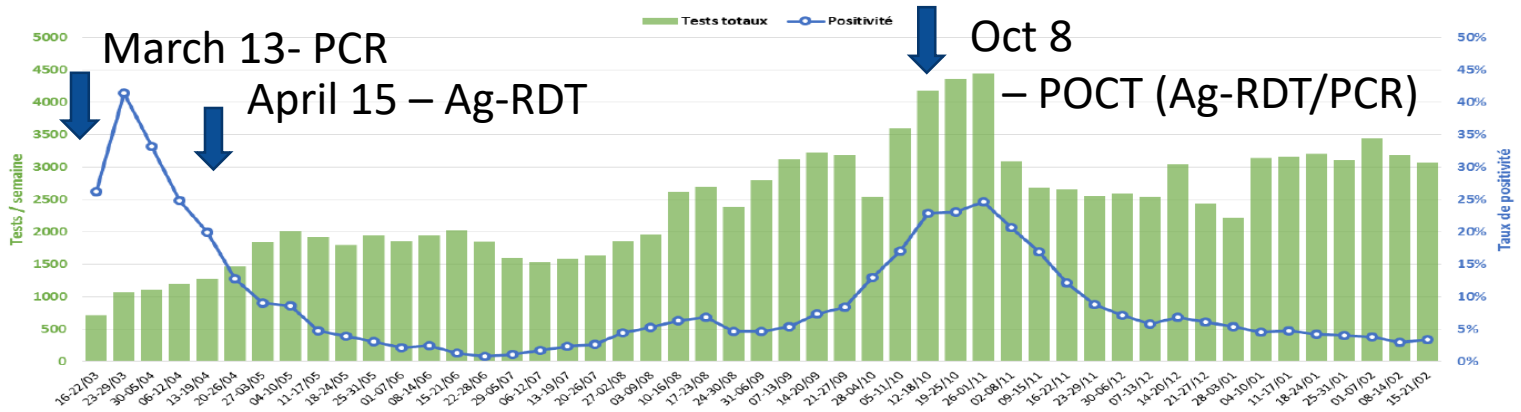
# Covid-19 Belgium Epidemiological Situation




**LHUB-ULB**

**Nb de tests/semaine**

**Taux de positivité**




1 March 2021

# Aims of COVID-19 Diagnostics and Testing

**Individual level**

- To confirm COVID-19 in symptomatic patients who present for care
- To rule out COVID-19 in asymptomatic patients who present for care
  - To appropriately manage suspected case and implement as soon as possible public health measures such as isolation or quarantine/cohorting.

**Public Health level**

- To screen contacts of confirmed COVID-19 cases
  - A large number of infected individuals may only have very mild symptoms or no symptoms at all but they can still shed virus and transmit infection.
  - Testing contacts of confirmed cases is critical in interrupting transmission of COVID-19 …. (nosocomial /community).
- To conduct rapid situation analysis and surveillance
  - To support the assessment of the effectiveness of control interventions
  - To monitor disease trends over time

# Laboratory diagnostic tools for COVID-19 suspected cases

- There are two major types of diagnostic tools that we can use for the pandemic response:
  - Direct diagnostic tests:
    - **Molecular tests** ⇔ detect viral RNA
    - **Antigen tests** ⇔ detect viral proteins
    - Culture ⇔ detect viable virus

  Different type of specimen: nasopharyngeal, narinal and/or throat swabs or saliva (with or without pooling)

  - Indirect diagnostic tests:
    - **Serology tests** to detect antibodies that patients develop in response to infection
    - Blood-based biomarkers

  Different type of specimen: human serum, whole blood or plasma

# Laboratory tests for SARS-CoV-2 direct detection and Potential Uses

| Ag RDTs | Rapid-NAATs | Automated Ag | Large PCR platform |
|---|---|---|---|
| • PoC-friendly<br>• Rapid result (15-30 min)<br>• Low throughput<br>• Lower Se<br>• Low cost | • PoC-friendly<br>• Rapid result (<1h)<br>• Low throughput<br>• High Se<br>• High cost | • In laboratory<br>• Rapid result (1-2h)<br>• High throughput<br>• Low cost<br>• Grey zone (ROC curve)<br>• Biosafety consideration | • « Gold » standard<br>• In laboratory<br>• ≈ 24-48 h<br>• High throughput<br>• High Se<br>• Shortages |

**Point of Care** **Laboratory**

# RT-PCR Large automated plateform "Gold" Standard

- Good global analytical performances
  - ! variants
- Meaning of Ct value?

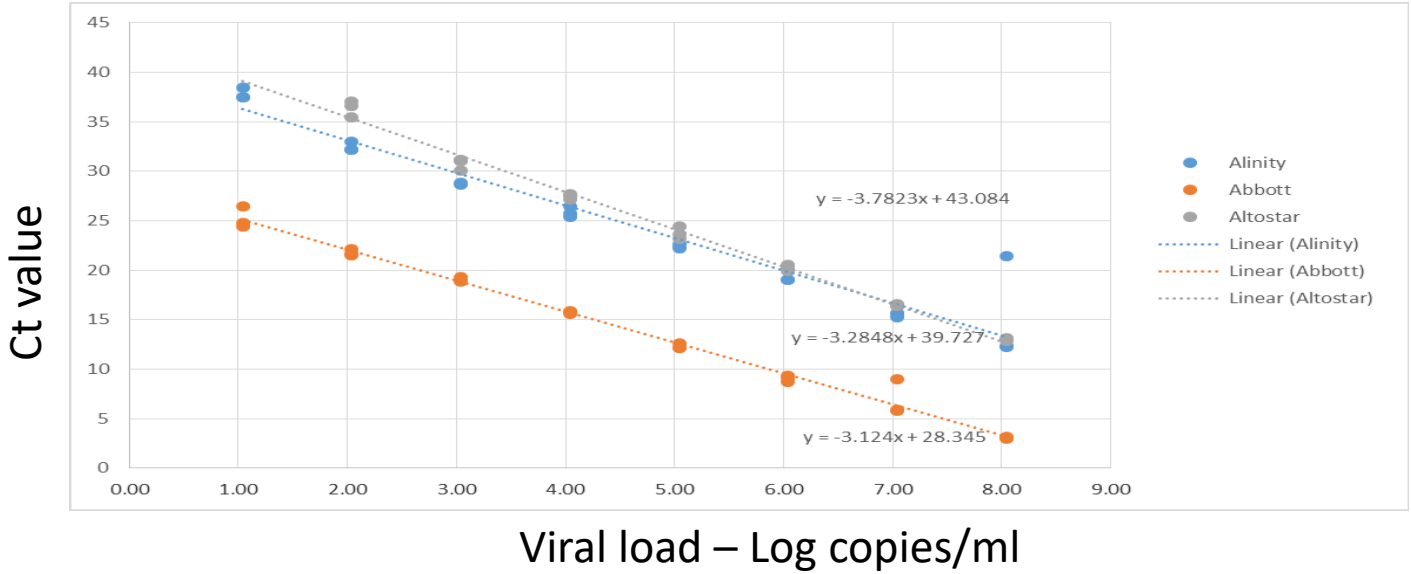
Use of cycle threshold ($C_t$) values as surrogate for calculated viral load in the management of patients?

| Assay | Number of laboratories | Number of gene targets | Genes targeted | Total datasets generated |
|---|---|---|---|---|
| GeneXpert (Cepheid, Sunnyvale, California, United States) | 6 | 2 | E gene<br>N gene | 12 |
| Logix Smart (Co-Diagnostics, Inc, Salt Lake City, Utah, United States) | 2 | 1 | RdRp gene | 2 |
| Cobas 4800 (Roche Diagnostics, Basel, Switzerland) | 2 | 2 | ORF1a/b<br>E gene | 4 |
| RealStar (Altona DiagnosticsGmbH, Hamburg, Germany) | 1 | 1 | E gene | 1 |
| genesig (Primerdesign, Southampton, Hants, United Kingdom) | 4 | 1 | ORF1a/b | 4 |
| RespiBio (Serosep, Limerick, Ireland) | 2 | 1 | RdRp gene | 2 |
| VIASURE (CerTest Biotec, Zaragoza, Spain) | 3 | 2 | ORF1a/b<br>N gene | 3 (2 genes combined) |
| Abbott Real*Time* SARS-CoV-2 (Abbott Park, Illinois, United States) | 1 | 2 | RdRp gene<br>N gene | 1 (2 genes combined) |
| Allplex SARS-CoV-2 (Seegene, Seoul, South Korea) | 1 | 3 | RdRp gene<br>N gene<br>E gene | 3 |

Carroll Anne, McNamara Eleanor. Comparison and correlation of commercial SARS-CoV-2 real-time-PCR assays, Ireland, June 2020. Euro Surveill. 2021

# RT-PCR Large automated plateform "Gold" Standard

- Meaning of Ct value?
  - No correlation between $C_t$ value and disease severity
  - Using $C_t$ values to influence patient management is complex and must be done with caution

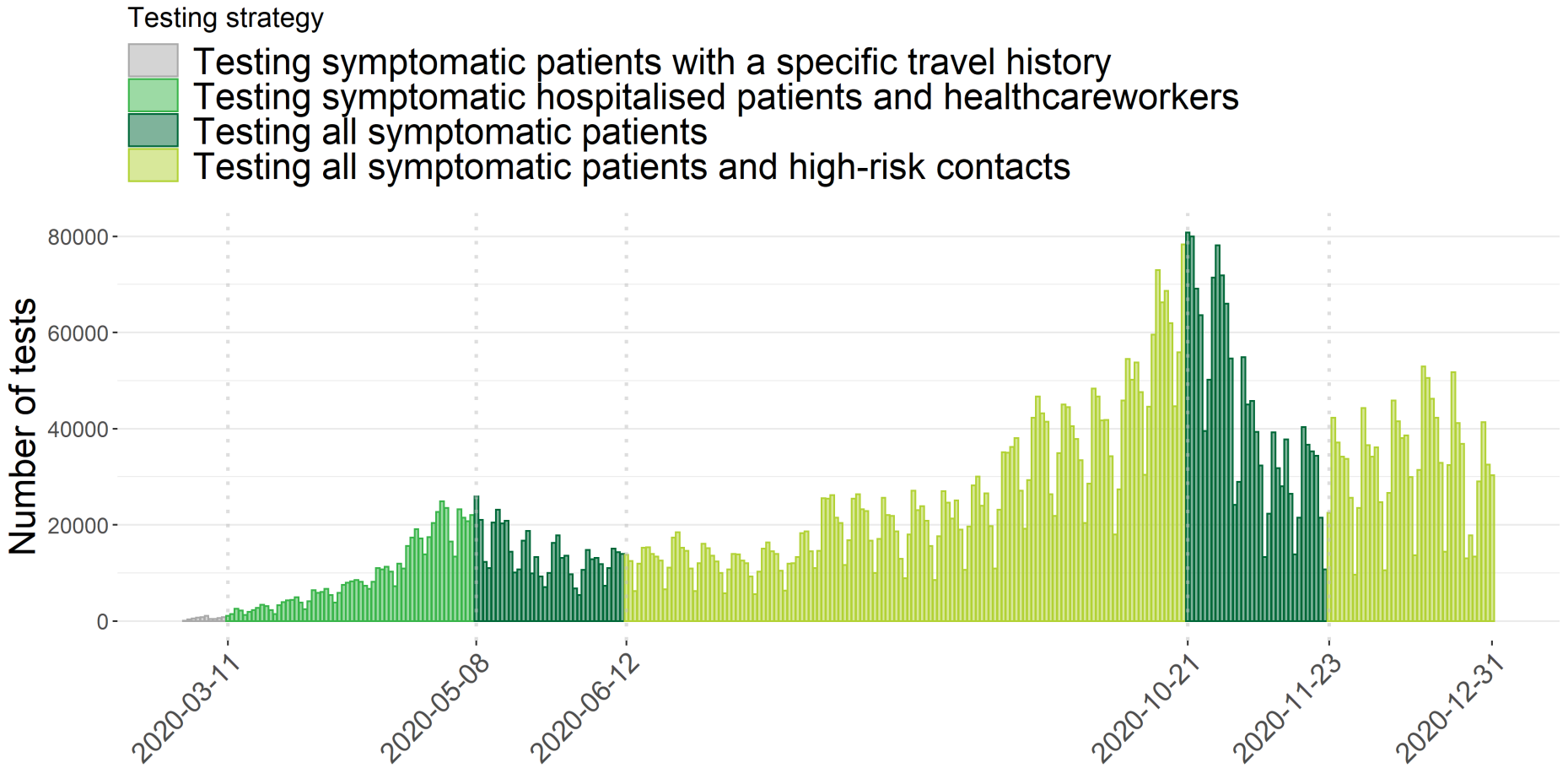



- Binary reporting => reporting of ranges ('high', 'medium', 'low') categories

**! Should be based on VL not on absolute $C_t$ values**

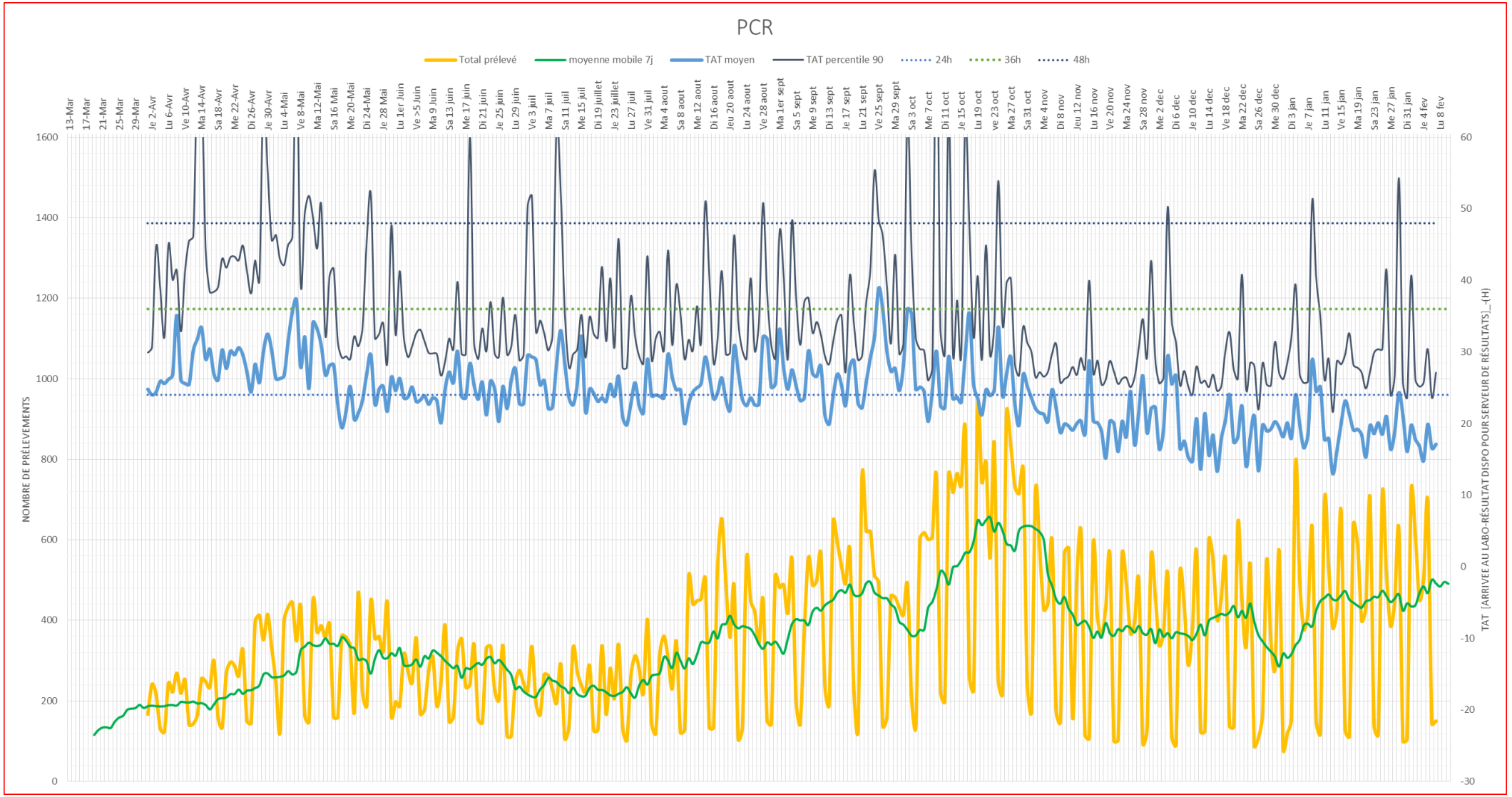
| | Très fort positif> | 10E7 copies> | Fort positif> | 10E5 copies> | Positif> | 10E3 copies> | Positif faible |
|---|---|---|---|---|---|---|---|
| Abbott m2000 | Le patient est contagieux | 6.5 | Le patient est probablement contagieux | 12.7 | Le patient est potentiellement contagieux, sauf s'il y a des preuves cliniques /sérologiques d'une infection ancienne résolue | 19 | Le patient n'est probablement pas ou plus contagieux s'il y a des preuves cliniques /sérologiques d'une infection ancienne résolue |
| Altona (Cov19 - S gene) | | 16.6 | | 24.2 | | 31.7 | |
| Alinity | | 16.7 | | 23.3 | | 29.9 | |

# COVID-19 diagnostic tests performed by the different testing strategies implemented from the March to December 2020

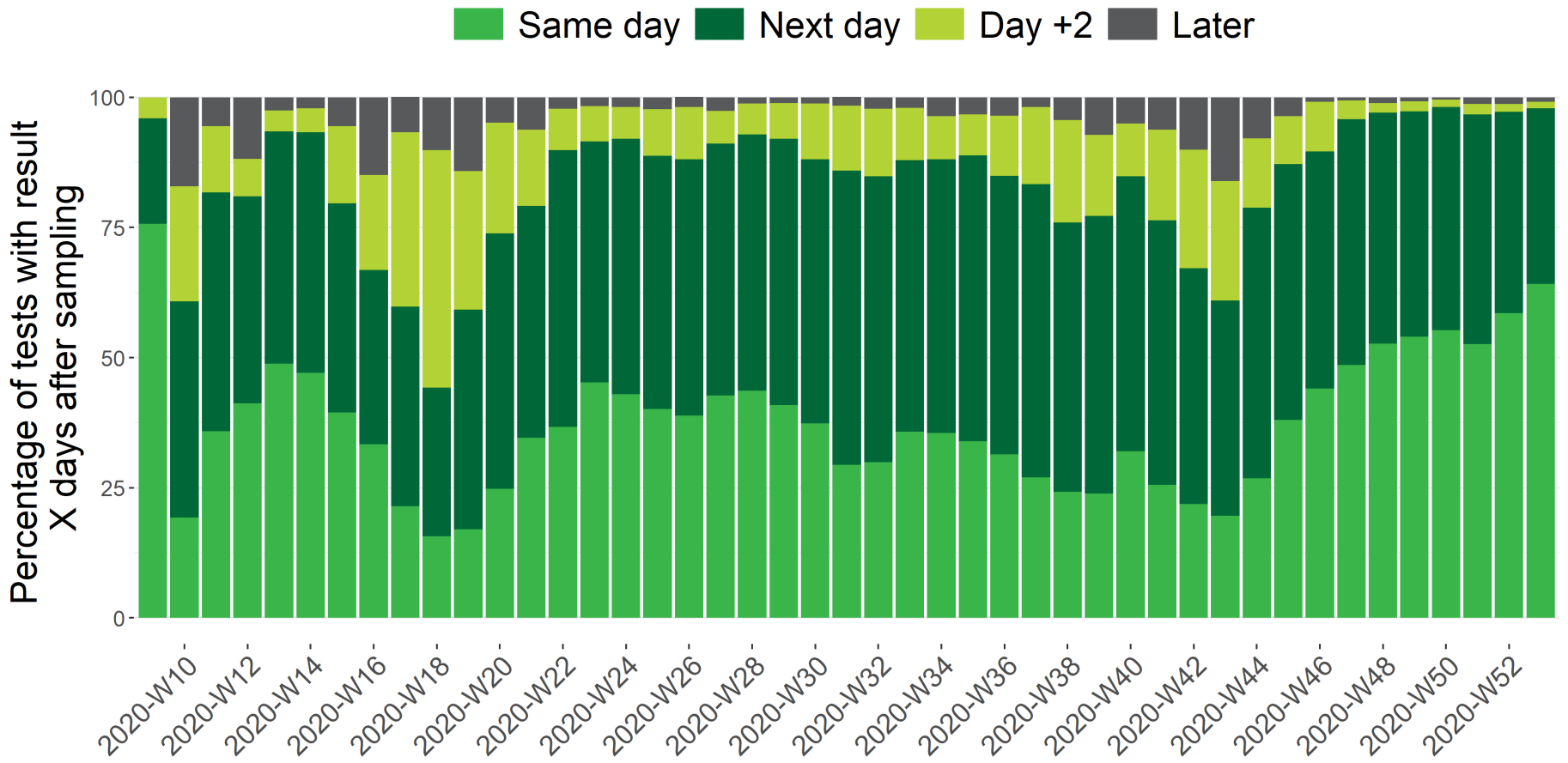



*Courtesy from Dieter Van Cauteren, Dpt Epidemiology and public health, Sciensano*

# Daily testing volume and TAT in the LHUB-ULB



# Weekly percentage of tests with a results within a given timeframe

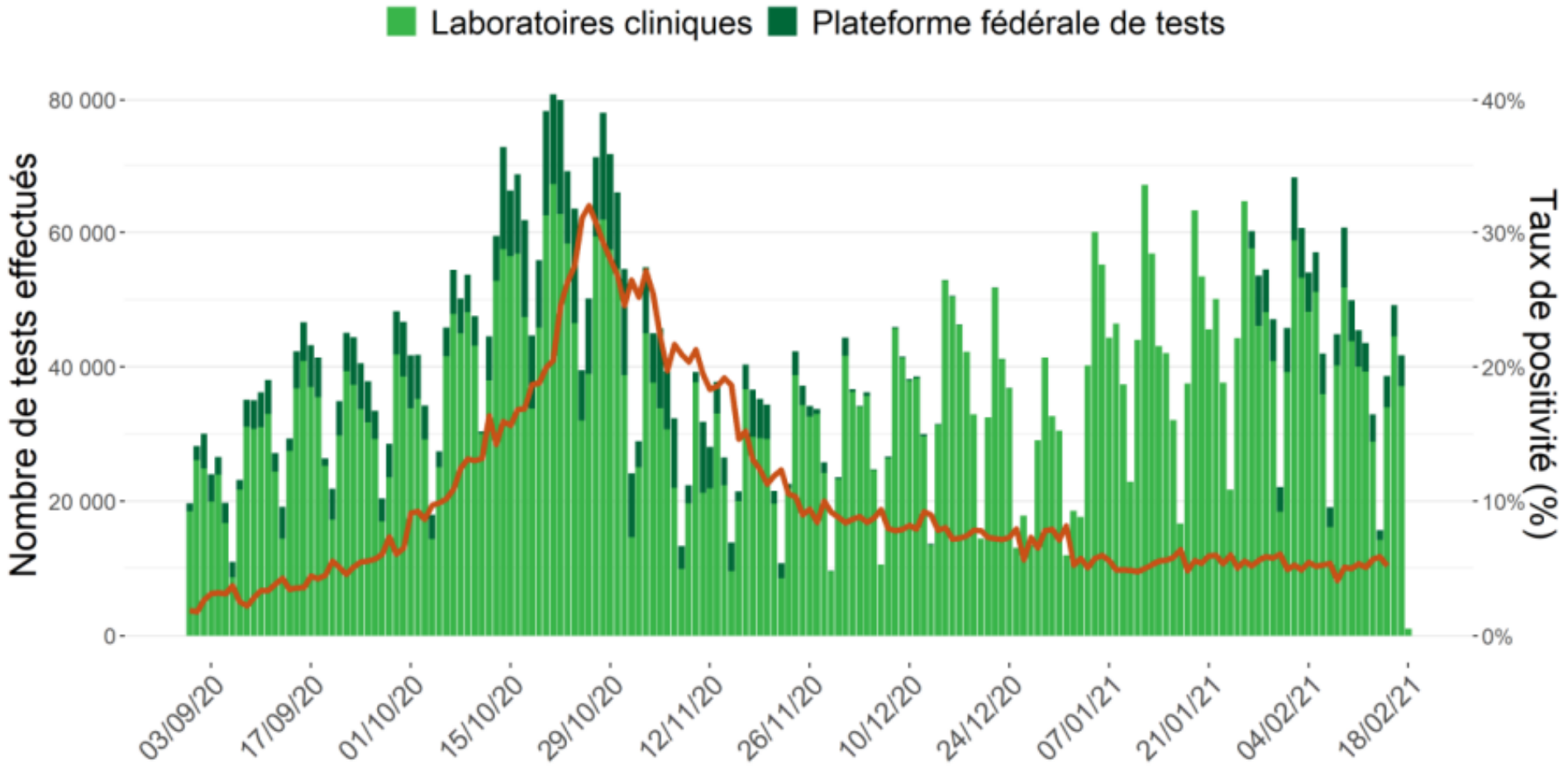



*Courtesy from Dieter Van Cauteren, Dpt Epidemiology and public health, Sciensano*

# Development and collaboration with industrial and/or academic platforms

- Mid-March 2020:
  - Set-up of a governmental working group (task force) to increase the testing capacity
  - This working group set up a parallel platform gathering some biotech/pharma industries and two universities (KU Leuven and the University of Liège).
- April 10th, 2020
  - Launch of these platforms essentially devoted to testing in homes for older people, nursing homes…… and later for triage centres.
- Mid-April 2020
  - LHUB-ULB supported UCB industrial platforms and ULB by providing EQC and review the quality of the process. Concerns about the pre-and post-analytical phases which were manual was raised.
  - A call for the wide use of the capacities (and skills) of the existing clinical biology laboratories was also launched.
- Mid-May 2020,
  - The samples from roughly 40 to 50% of the triage centres were analysed on the federal platform
- From April 10 to July
  - 381.234 (32,3%) tests were performed by the Federal plateforms whereas 797 487 (67,7%) tests were performed by routine clinical labs (from March to June 25th, 2020).

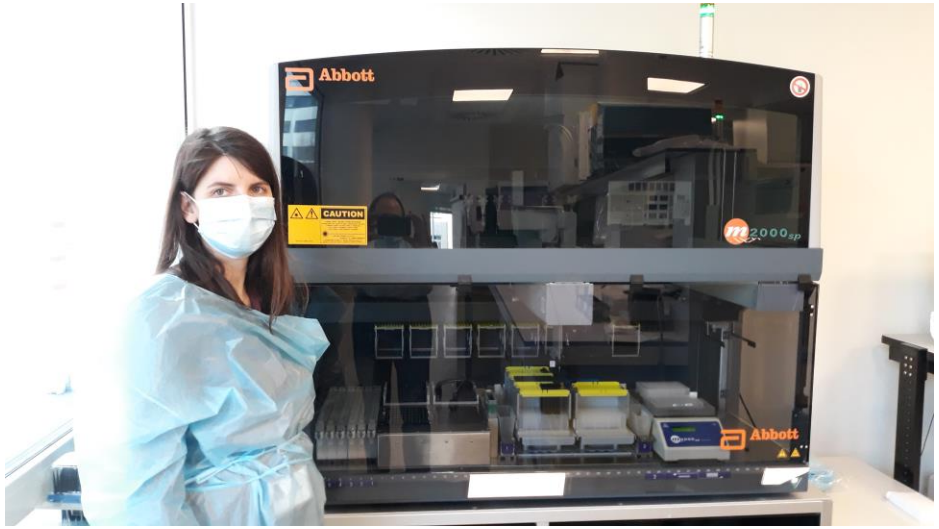
# Number of COVID-19 diagnostic tests reported in Belgium

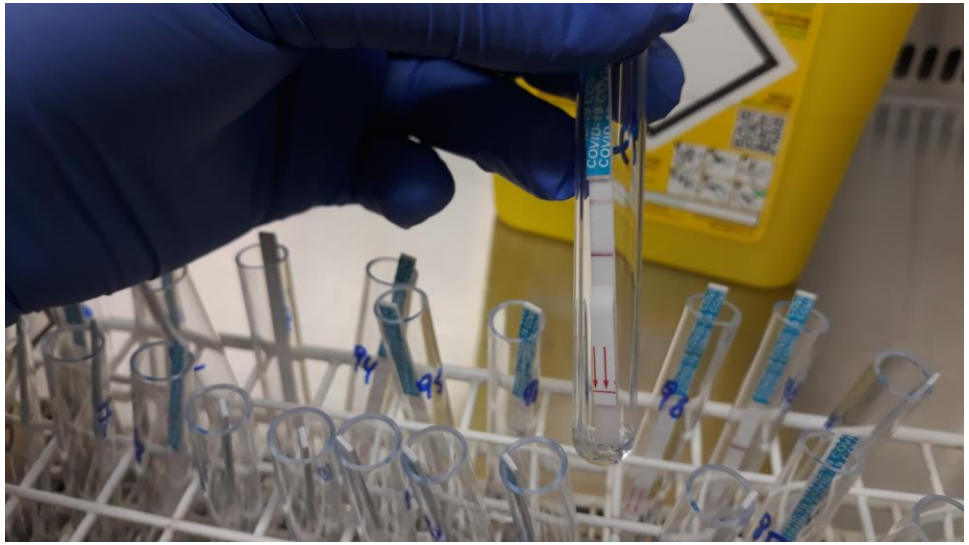


# Reimbursement of testing

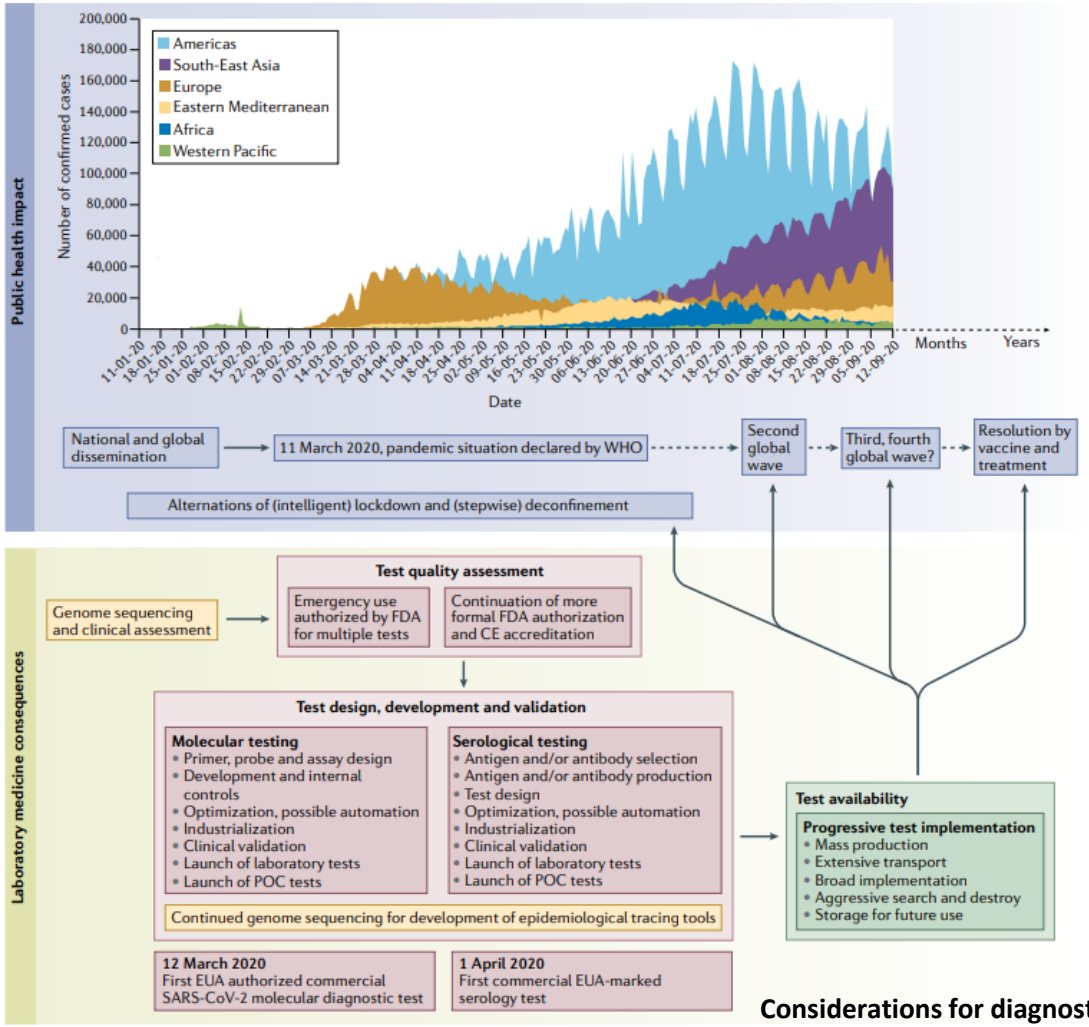
| € / Analyse | Début Pandémie | 2020 | 2021 |
|---|---|---|---|
| Réactif et Disp | 35 | 26 | 20 |
| Personnel | 23 | 8 | 8 |
| EPI | 2 | 1,5 | 1,5 |
| Maintenance | 3 | 2 | 2 |
| Prélèvement | 27 | 15 | 10 |
| Frais Fixe | 10 | 10 | 10 |
| Total | 100 | 62,5 | 51,5 |
| Rbt | 46,81 | 46,81 | 47,18 |

# Mass production of tests: Supply chain failure



# Mass production of tests: Supply chain failure




**Considerations for diagnostic COVID-19 tests**
Vandenberg O. Nat Rev Microbiol. 2021. doi: 10.1038/s41579-020-00461-z

**Mass production of tests**

Infectious disease outbreaks tend to be categorized as low-frequency, high-impact supply chain-disruptive events[76]. They represent a supply chain risk characterized by long-term disruption and unpredictable scaling; simultaneous disruption in the supply chain (for example, manufacturing) and the population (for example, pandemic); and simultaneous disruptions in supply, demand and logistic infrastructure[77]. This disruption was palpable for COVID-19 diagnostic tests both in the manufacturing disruption observed and in the downstream logistics infrastructure delivering diagnostic tests to the end users. The tight interoperability of the supply chain as well as the initial (physical and economic) lockdown of China, representing a low-tier supply base for a large part of the manufacturing operations globally, meant that manufacturing would be one of the hardest-hit economic sectors[78,79]. Therefore, a dual bottleneck emerged early on in the pandemic in terms of sourcing the biological materials as well as sourcing the primary sources for manufacturing. The shortage of reagents and disposables is one of the most obvious later-stage problems once an outbreak becomes more widespread and ultimately pandemic[80,81]. In such instances it may become mandatory for manufacturers to start sharing production processes and recipes for reagents[82].

A number of governmental interventions, including direct financial investments, loans and the appointment of special COVID-19 functionaries (with responsibilities for obtaining tests, instruments, vaccines and informing the public, among functions) and policymakers, were initiated to support manufacturing capacity. In the USA, congressional lawmakers introduced legislation to alter the regulatory framework governing laboratory-developed tests[83]. The interventions further included active scouting and import of resources outside usual territories, the continued operation of manufacturing businesses, mobilization towards critical supplies, including the repurposing of manufacturing capacity, and planning for further support in the post-COVID-19 era[84,85]. However, the rapid publication of formal guidelines does not necessarily equate to an increased production capacity for diagnostic tests, as the production of such tests tends to have a particular technological specification and complex manufacturing, and thus manufacturing flexibility and scalability are harder to achieve[86,87]. During a pandemic, the disease burden limits the availability of personnel, and the need to work under protected conditions (masks and suits) does not promote

# “1st generation” RDT

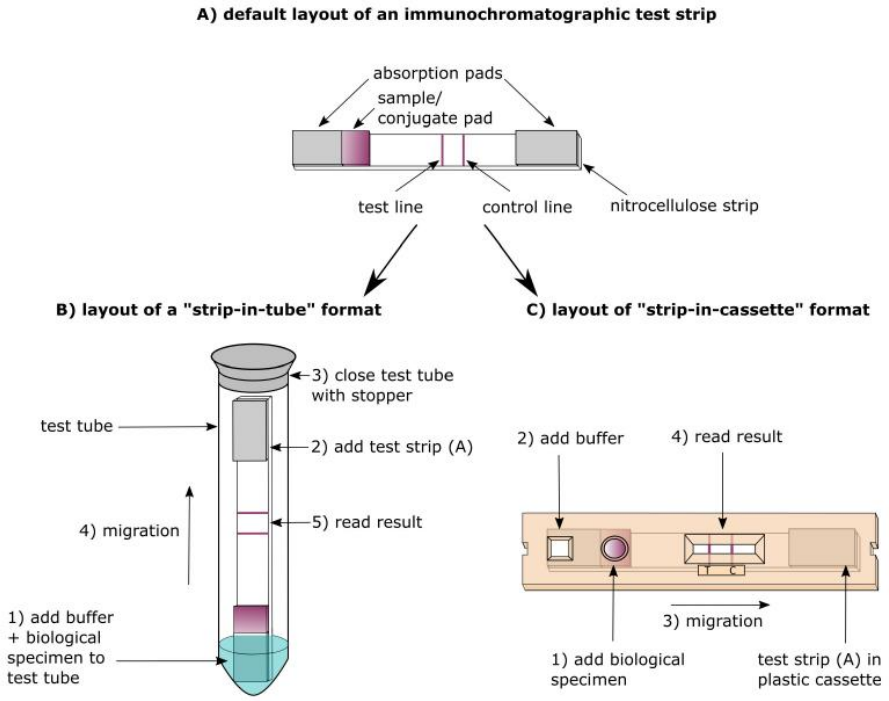
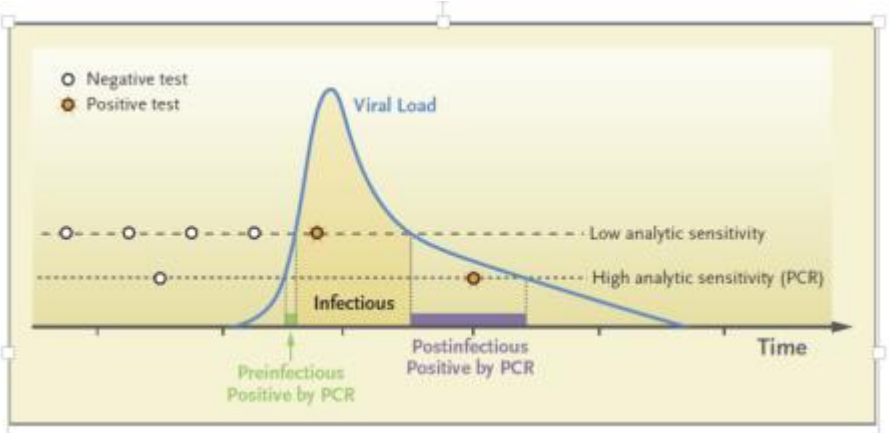



FIGURE 1 | Design and principle of antibody vs. antigen detection lateral-flow immunochromatography assays (LFIA).

**Development and Potential Usefulness of the COVID-19 Ag Respi-Strip Diagnostic Assay in a Pandemic Context.** Mertens and al. Frontiers

- Belgium was one of the first country to develop and to use them with an emergency authorization of use
- Used on a routine basis during the decrease of the 1st wave
- Used in laboratories on non selected UTM samples
- Criticized for a low sensitivity around 57.6% compared to PCR despite an excellent PPV (better with high viral load)



# Application procedure for manufacturers seeking a recommendation of antibody or antigen tests during the COVID-19 outbreak in Belgium.

## 20201105_Advice RAG_Ag RDTs in ambulatory care_FR.pdf

la durée des symptômes et la probabilité de pré-test. De plus, la plupart des études réalisées à ce jour ont évalué les tests dans des conditions de laboratoire idéales, et on sait peu de choses sur leurs performances dans un contexte (*point of care*) réel. Il faut donc veiller à choisir correctement le test à utiliser. L'OMS recommande des Ag RDT qui répondent aux exigences minimales de performance de ≥80% de sensibilité et de ≥97% de spécificité par rapport à la RT-PCR (voir les conseils de l'OMS sur les tests rapides antigéniques). Dans les milieux où la prévalence est faible, une spécificité de 99 % est recommandée.

Nous recommandons :

- D'avoir au moins une évaluation indépendante du test en situation réelle, avec une population répondant aux critères décrits ci-dessous (patients dont la durée des symptômes est de 5 jours maximum) ;
- De suivre la recommandation de l'OMS et ne jamais utiliser de tests ayant une sensibilité inférieure à 80 % ou une spécificité inférieure à 97 % ;
- d' idéalement utiliser le seuil souhaitable de sensibilité minimal de 90% pour les cas symptomatiques avec apparition récente des symptômes (voir plus loin).

Autres questions à prendre en compte dans le choix des Ag RDT:

- Un temps de lecture de 20 minutes maximum ;
- Si des lecteurs automatisés sont nécessaires, ils doivent être transportables et utilisables hors réseau ;
- Un niveau de complexité limité nécessitant une formation minimale, c'est-à-dire moins de 2 heures avec mode d'emploi et guide(s) de référence rapide ;

## FAMHP: Eligibility criteria for SARS-CoV-2 antigen tests

| | |
|---|---|
| **Precision** | Both repeatability and reproducibility should be assessed. |
| **Cut-off value** | If applicable, provide a rationale for the chosen cut-off value. |
| **Clinical sensitivity** | ≥ 90 % (with 95 % confidence intervals).<br>Comparison with a validated molecular test using nasopharyngeal samples should be performed. If possible, specify the range of Ct-values that correspond to antigen test sensitivity values (e.g. sensitivity for Ct≤25 and sensitivity for Ct>25). Indicate during which period (days after symptoms onset) samples should be taken. |
| **Clinical specificity** | ≥ 99 % (with 95 % confidence intervals). |
| **Controls** | Rapid tests[1] shall include a procedural control detecting the capability of the assay.<br>Other tests: when not included in the kit, specify which external controls have been validated and indicate within which predetermined limits control results should fall. |
| **Instrumentation** | If applicable, indicate what instrumentation and software is needed to run/read the test and provide at least one validated combination for tests that can be run/read on multiple platforms. |

# “2nd generation” RDTs

Veritor SARS-CoV-2 POC test

*Young et al., 2020*

TABLES
TABLE 1

**Table 1.** Veritor test performance at one through seven DSO

| Performance[a] | 1 DSO | 2 DSO | 3 DSO | 4 DSO | 5 DSO[b] | 6 DSO | 7 DSO |
|---|---|---|---|---|---|---|---|
| **PPA** %, [95% CI] | 87.5 [52.9, 97.8] | 85.0 [64.0, 94.8] | 81.8 [61.5, 92.7] | 85.2 [67.5, 94.1] | 83.9 [67.4, 92.9] | 82.4 [66.5, 91.7] | 76.3 [60.8, 87.0] |
| **NPA** %, [95% CI] | 100 [88.6, 100] | 100 [95.1, 100] | 100 [97.1, 100] | 100 [97.7, 100] | 100 [98.1, 100] | 99.5 [97.4, 99.9] | 99.5 [97.4, 99.9] |
| **OPA** %, [95% CI] | 97.4 [86.5, 99.5] | 96.8 [91.1, 98.9] | 97.3 [93.3, 99.0] | 97.9 [94.7, 99.2] | 97.8 [94.9, 99.1] | 97.1 [94.2, 98.6] | 96.0 [92.8, 97.8] |
| **AUC** | 0.94 | 0.93 | 0.91 | 0.93 | 0.92 | 0.91 | 0.88 |
| | | | | **True positives** | | | |
| **Incident** | 7 | 10 | 1 | 5 | 3 | 2 | 1 |
| **Cumulative** | 7 | 17 | 18 | 23 | 26 | 28 | 29 |
| | | | | **False negatives** | | | |
| **Incident** | 1 | 2 | 1 | 0 | 1 | 1 | 3 |
| **Cumulative** | 1 | 3 | 4 | 4 | 5 | 6 | 9 |
| | | | | **True negatives** | | | |
| **Incident** | 30 | 45 | 52 | 35 | 33 | 15 | 2 |
| **Cumulative** | 30 | 75 | 127 | 162 | 195 | 210 | 212 |
| | | | | **False positives** | | | |
| **Incident** | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| **Cumulative** | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| **Total** | **38** | **95** | **149** | **189** | **226** | **245** | **251** |

**Abbreviations:** DSO, days from symptom onset; PPA, positive percent agreement; NPA, negative percent agreement; OPA, overall percent agreement; AUC, area under the curve

[a]Performance of Veritor test compared to the Lyra assay as reference
[b]The Veritor test is FDA-authorized for detection of SARS-CoV-2 only in individuals that are 0-5 DSO


- Developed by diagnostics major players (Abbott, BD…)
- Only symptomatic patients since less than 7 days
- Use of dry swabs in a Point-of-Care setting

→ Better performances or better target definition?

# Assessing RDTs performances at the frontline

- Setting:
  - At the ER of Saint-Pierre hospital
  - At a local diagnostic center organized by a group of GPs
- Recommendations of sampling:
  - Maximum 7 days since symptoms onset (DSO) according to Sciensano case definition
  - Patients were informed beforehand that a negative result needed a new sampling for PCR

| | N | Se | IC95 | False negative median $C_T$ (range) |
|---|---|---|---|---|
| Overall | 494 | **83.2%** | 78.2-87.4% | 17.60 (4.93-29,02) |
| Veritor™<br>*- GPs*<br>*- ER* | 18<br>3<br>*111*<br>*72* | **87.7%**<br>***87.3%***<br>***88.2%*** | 80.1-92.7%<br>*76.0-93.7%*<br>*76.6-94.5%* | 15.46 (**4.93***-18.54) |
| Coris | 140 | **80.0%** | 69.2-87.7% | 21.56 (15.52-29.02) |
| Panbio™ | 102 | **80.8%** | 68.1-89.2% | 18.32 (10.29-23.68) |
| Biosensor ™ | 69 | **78.2%** | 58.1-90.3% | 15.53 (14.92-16.15) |
| DSO ≥ 5 | 56 | **63.6%** | 46.6-77.8% | 15.46 (4.93-27.02) |
| DSO <5<br>*- 0-1 DSO*<br>*- 2 DSO*<br>*- 3 DSO*<br>*- 4 DSO* | 40<br>4<br>*98*<br>*122*<br>*120*<br>*64* | **86.9%**<br>***89.1%***<br>***90.3%***<br>***80.3%***<br>***89.3%*** | 81.6-90.8%<br>*78.2-94.9%*<br>*80.5-95.5%*<br>*68.7-88.4%*<br>*72.8-96.3%* | 18.38 (10.90-29.02) |

*Outlier: Sampling failure?

# COVID-19 Ag Respi-Strip - Coris BioConcept

| Date | Events |
|---|---|
| March 24, 2020 | COVID-19 Ag Respi-Strip : CE marked |
| April , 2020 | COVID-19 Ag Respi-Strip : FAMHP Approval |
| September 09, 2020 | Adapted data sent to FAMHP |
| November 2020 | Withdrawal of COVID-19 Ag Respi-Strip of the FA… **…eimbursement and no prior information to Coris** |
| November 6th, 2020 | Mail from the LHUB-ULB to FAM… …ngoing studies' results. FAMPH never answered our mail. Imm… …e head of Testing Task Force. |
| November 11, 2020 | New Submissi… … > 99% with dry swabs. Adapted intended use |
| December 2020 | C… …y provided by Coris) and interference substances. These additional … not in the requested criteria. Last reply from Coris : December 22, 2020 |
| January | …, 18, 26/01; mails and phone calls) with no answer. |
| Febru… | …n request for removing all information mentioning Se < 90% |
| Februa… | New submission with new CE marking for a new product only for Belgian market without UTM and GPs data. |
| February … | FAMHP APPROVAL |
| February 24, 2021 | COVID-19 Ag Respi-Strip Listed |

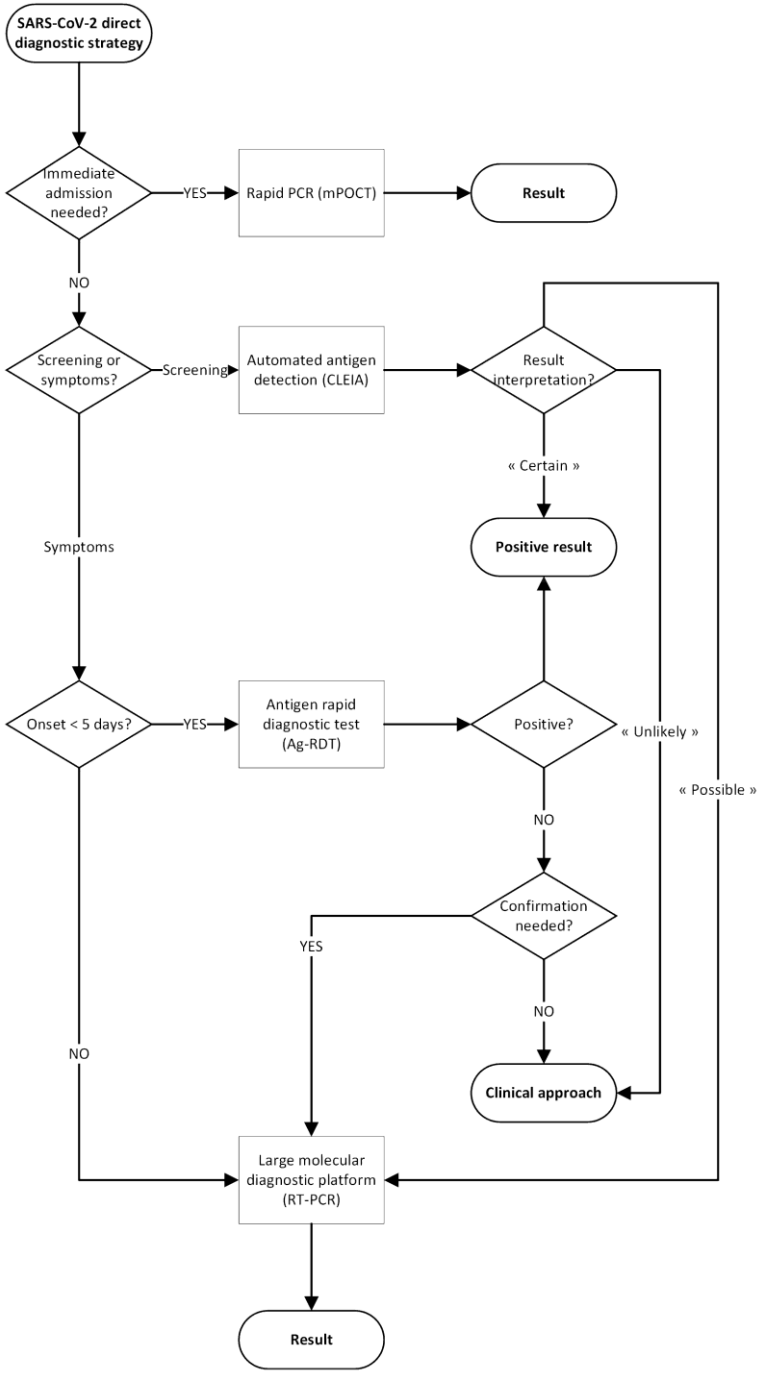
Currently, half (27/53) of the tests recommended by the FAMHP are of Chinese or Korean origin.
This is the opposite of what was supported on May 20, 2020 by the political world which underlined the absolute need to refocus critical supplies in Europe and if possible in Belgium.

# Automated antigen detection

Not yet implemented in routine due to the lack of reimbursement by social security

- Principles:
  - Quantitative dosing of specific viral proteins by immunoassay
  - Use of UTM samples
  - Use of biochemistry/serology laboratory instruments
  - Theoretical time to result around 30-60 minutes

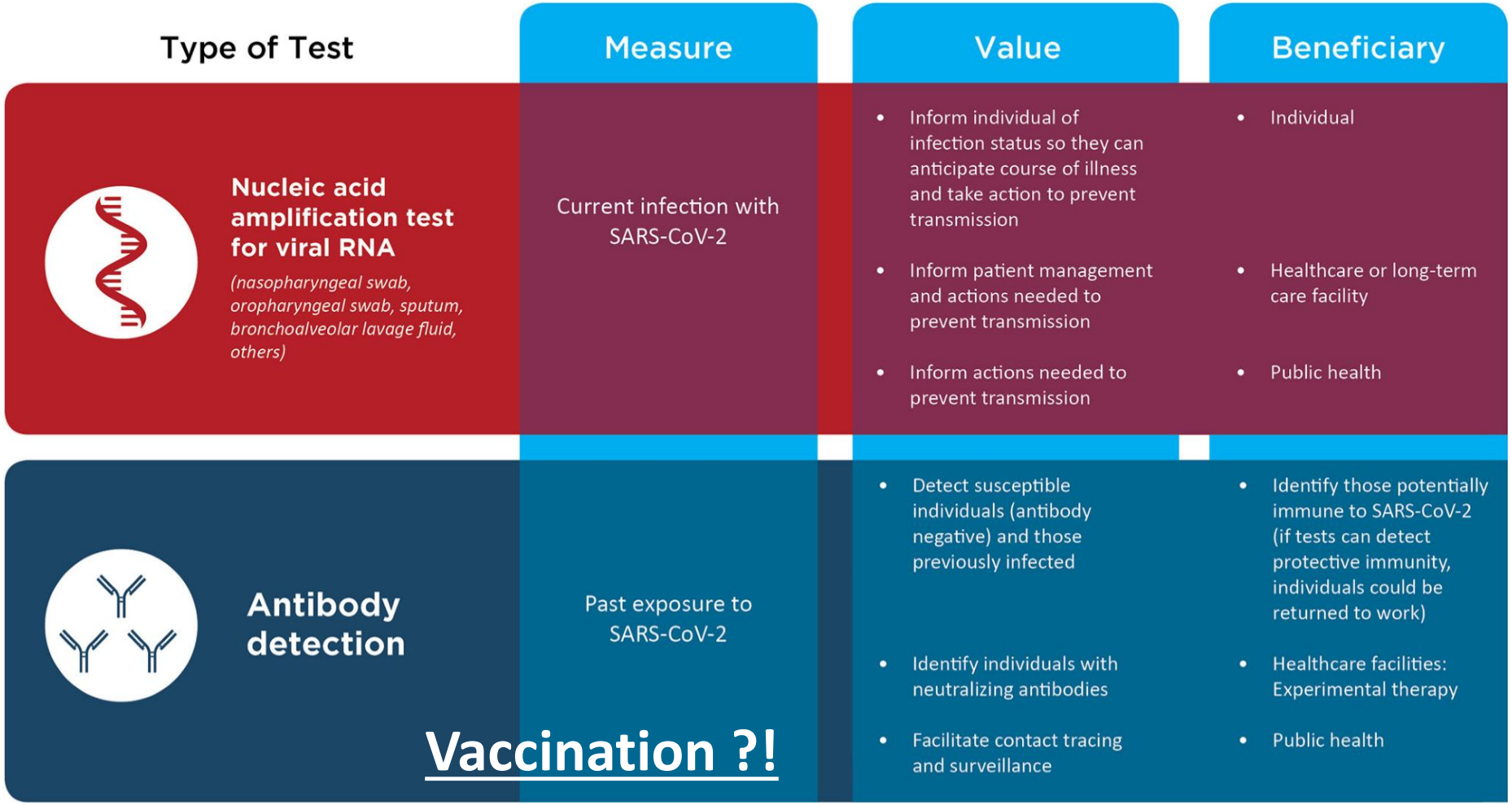
# Towards an integrated COVID-19 diagnostic algorithm




- **Using all the diagnostic techniques available to:**
  - Improve the time-to-result
  - Enlarge our testing capabilities
  - Better assess the infectiousness
  - Decrease our dependence on a few instruments (shortages)

- **Provide a reliable and accurate result for the physician and the patient**

# Laboratory tests for SARS–CoV-2/COVID-19 and Potential Uses




Patel R, mBio. 2020 Mar 26;11(2). pii: e00722-20. doi: 10.1128/mBio.00722-20.

LHUB-ULB

# COVID-19 surveillance studies: Moving toward an Integrated Real-Time Epidemiological Surveillance and Alert Based on Laboratory Data

HUDERF

CHU St-Pierre

Hôpital Erasme

Bordet

Population density #

> 000

< habitants

Moyenne régionale : 7057,00

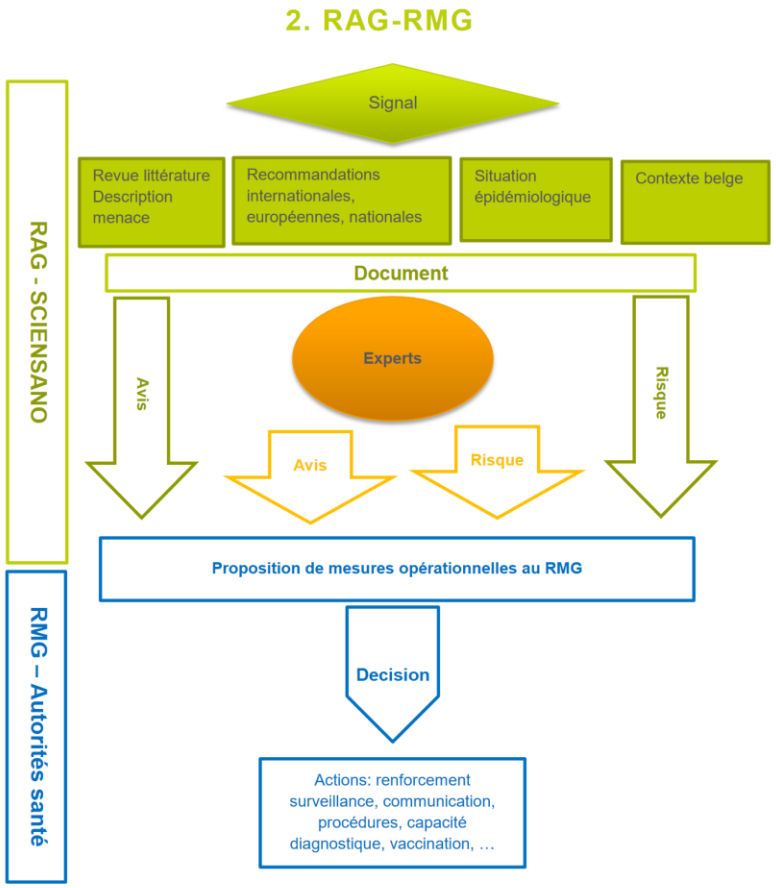
N

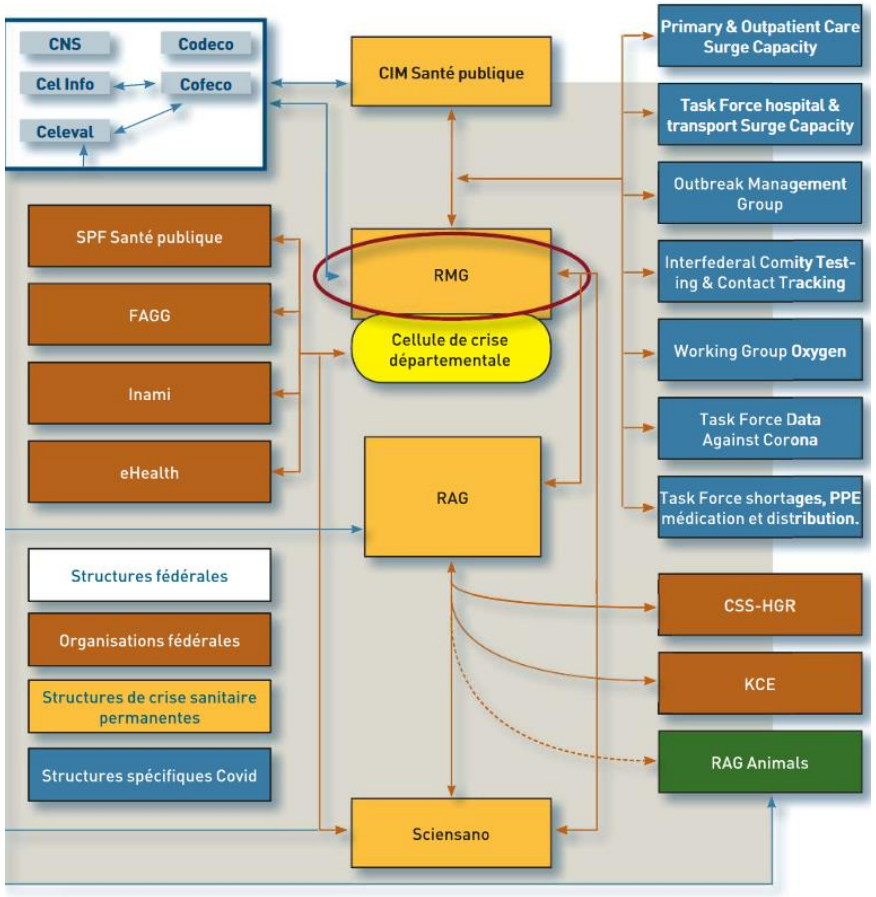
1 km

1 mi

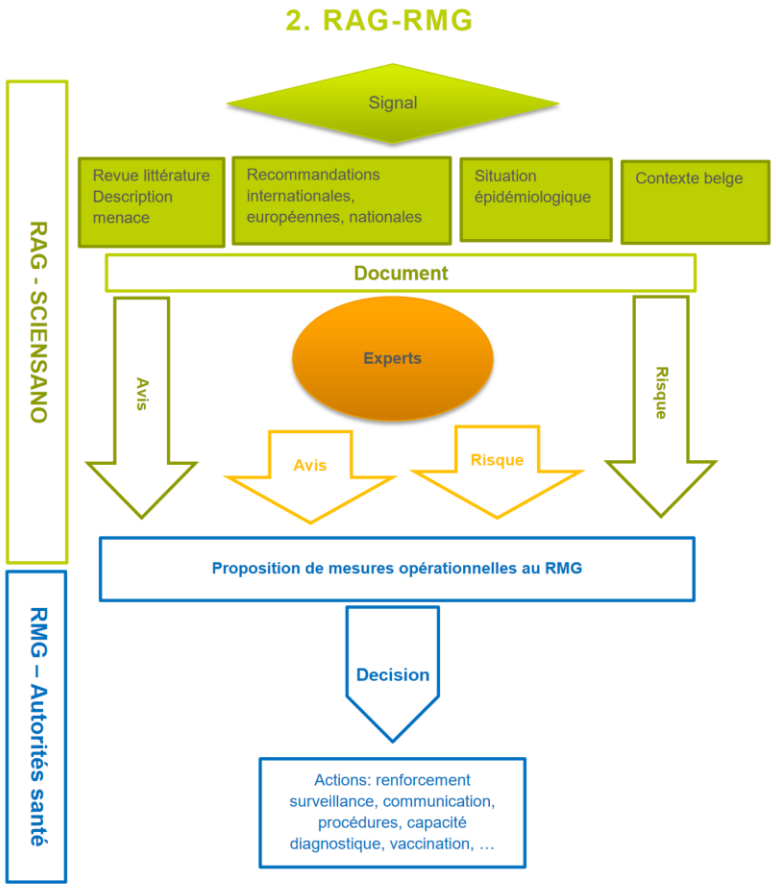
*Source : IBSA, SPF Economie – Direction générale Statistique – Statistics Belgium. Monitoring des Quartiers – IBSA Brussels UrbIS*

# Contribution of Laboratory medicine specialists in the public health response

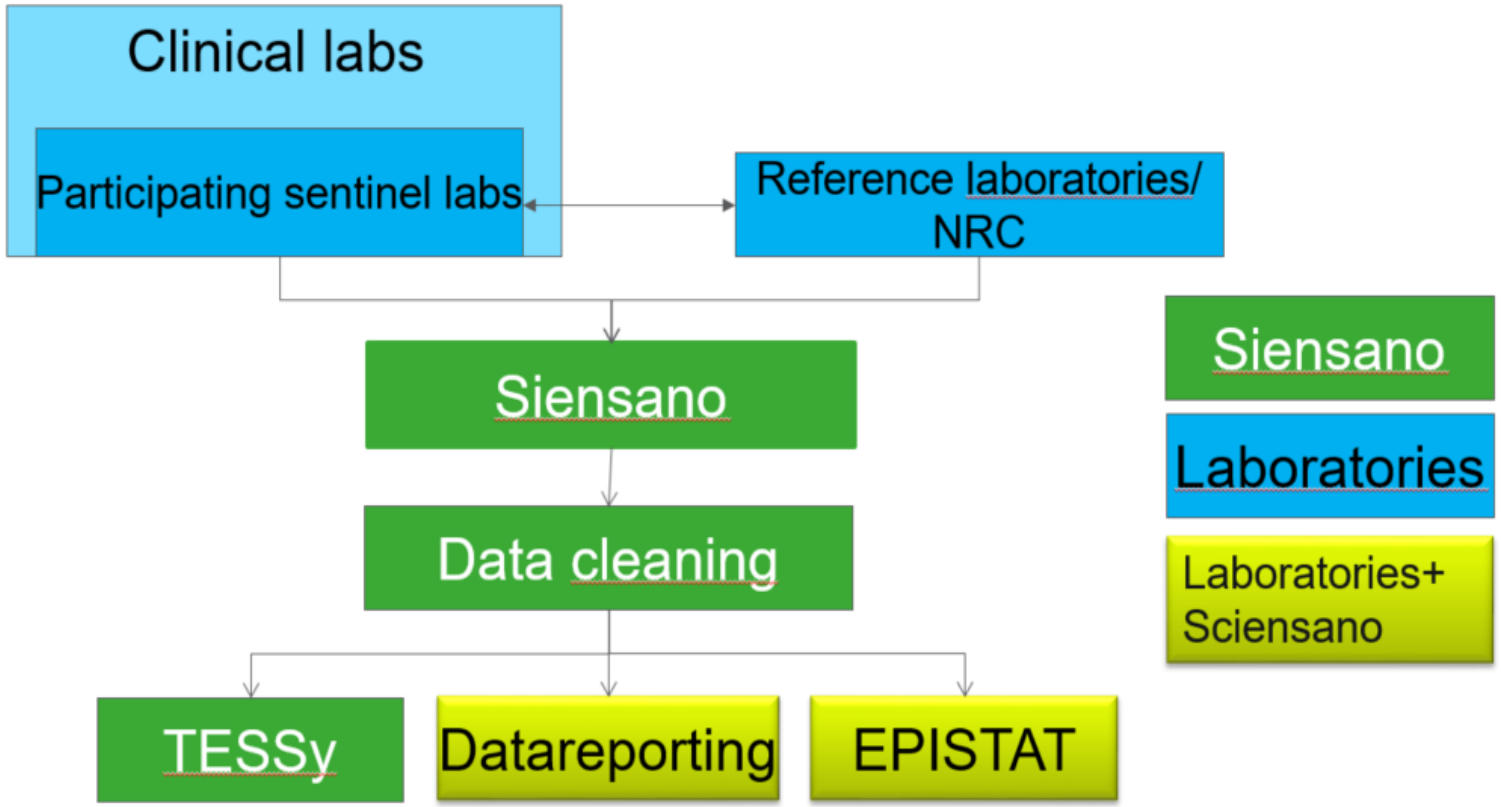


# Contribution of Laboratory medicine specialists in the public health response




# Sentinel laboratories network: a tool for surveillance




| Variables | |
|---|---|
| Patient ID | Date of birth<br>Sex<br>Postcode |
| Sample | Sample type<br>Sample code<br>Sample date (diagnosis) |
| Method | Type of test |
| Result | Pathogen<br>Type |
| Other | Country of infection |

*Courtesy from Dieter Van Cauteren, Dpt Epidemiology and public health, Sciensano*

# Belgian Sentinel Laboratory Network


The registration by the laboratories is continuous with daily real-time feedback through an electronic programme (Epi-Lab) or by Internet, or by weekly paper reporting. .

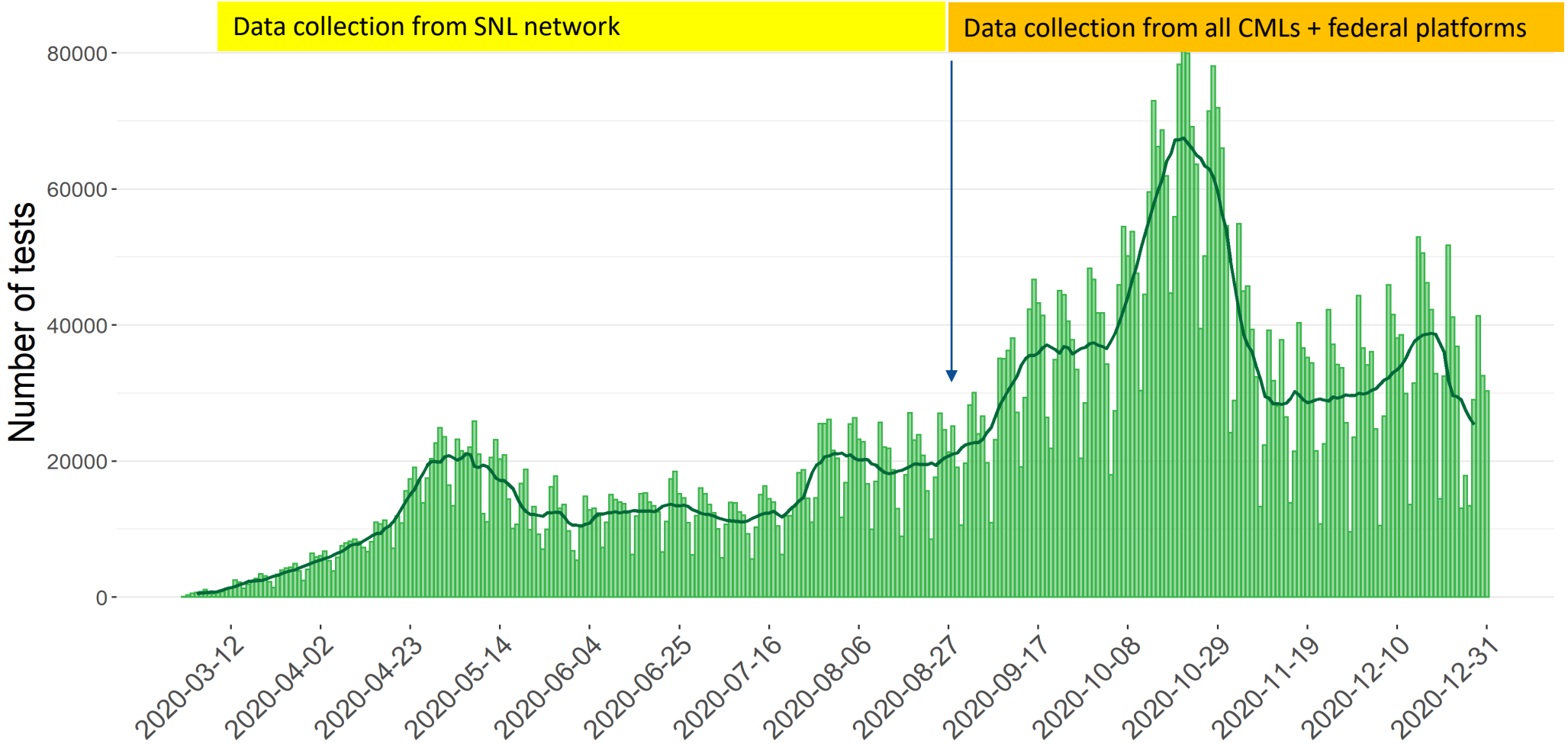
| | 2017 | 2018 | 2019 |
|---|---|---|---|
| Flanders | 53% | 53% | 59% |
| Brussels | 58% | 58% | 58% |
| Wallonia | 46% | 43% | 21% |
| Belgium | 52% | 51% | 47% |

**LHUB-ULB as sentinel lab:**
Between 1993-2019: 98,967/1,040,255 ≈ 9,5%

The SLN is a sentinel of about 83 voluntary, unpaid Microbiology labs representing 47% of all in 2019 certified private or hospital microbiology laboratories situated in 33 of 43 Belgian districts.

Assessing the sensitivity and representativeness of the Belgian Sentinel Network of Laboratories using test reimbursement data
Nicolas Berger et al. *Archives of Public Health* volume 74, Article number: 29 (2016)

# Number of COVID-19 diagnostic tests reported in Belgium




*Courtesy from Dieter Van Cauteren, Dpt Epidemiology and public health, Sciensano*

# Genomic surveillance of SARS-CoV-2 in Belgium

- Genomic surveillance in Belgium is restricted to designated sequencing platforms monitoring the emergence and the further spread of specific viral populations (variants of concern, VOCs) which may impact disease control and/or vaccination strategies.
- The genomic surveillance strategy comprises
  - baseline genomic surveillance: unbiased selection of positive samples from 24 sentinel labs (selected based on geographical dispersion and diversity of clinical patterns)
  - sequencing of additional priority samples
  - additional samples in specific situations.

| Indication | Number per week | Observation |
|---|---|---|
| Baseline genomic surveillance | +/-300 | Assuming current incidence remains stable |
| Atypical PCR results | +/-400-500? | To be confirmed<br>Overlap with other indications |
| Other additional priority samples | ? | Expected to be low |
| Cluster outbreaks | >250 | Currently high demand<br>Expected to decrease with vaccination roll-out |
| Returning travelers | +/-500 | Probably with important fluctuations |

# Genomic surveillance of SARS-CoV-2 in Belgium

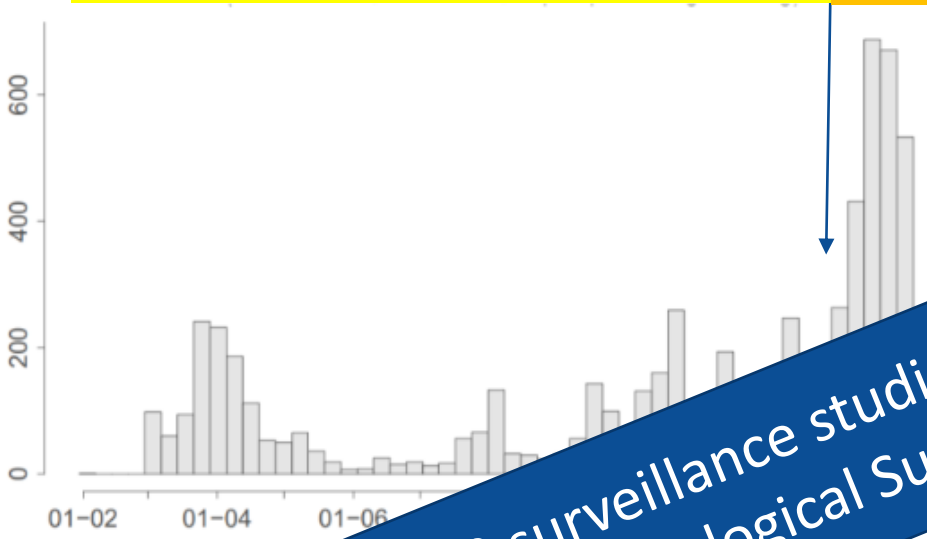
Report of the National Reference Laboratory (UZ Leuven & KU Leuven)

**Situation update – 23th of February 2021**
**(report 2021_13)**

7-10 days to
results a

Sequencing restricted to NRC

Restricted to federal platforms
No reimbursement for clinical labs



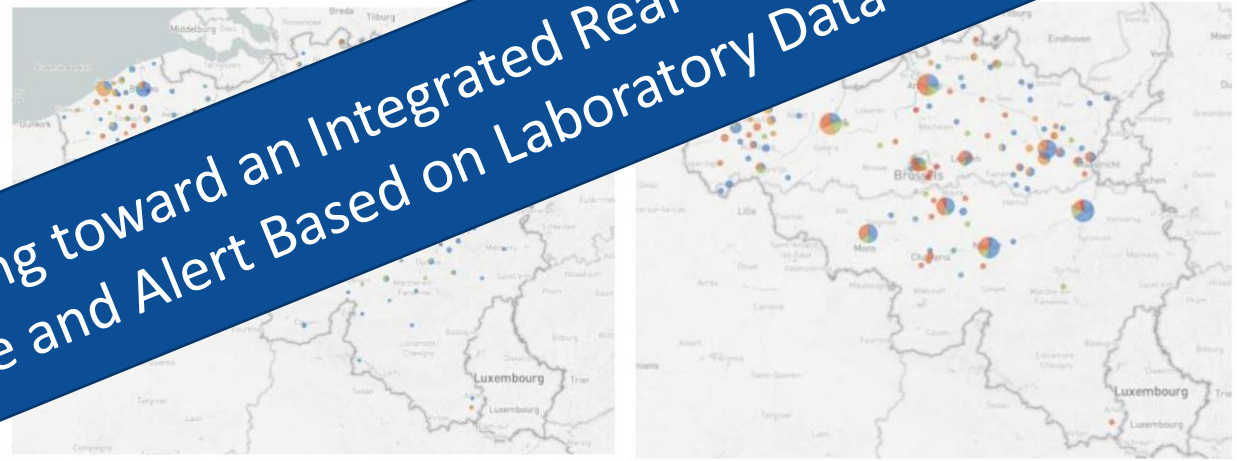




**Figure 1:** Representation of the geographical coverage of the genomic surveillance network in Belgium since February 2020 (left) and 1st of January 2021 (right).

COVID-19 surveillance studies: Moving toward an Integrated Real-Time Genomic Epidemiological Surveillance and Alert Based on Laboratory Data

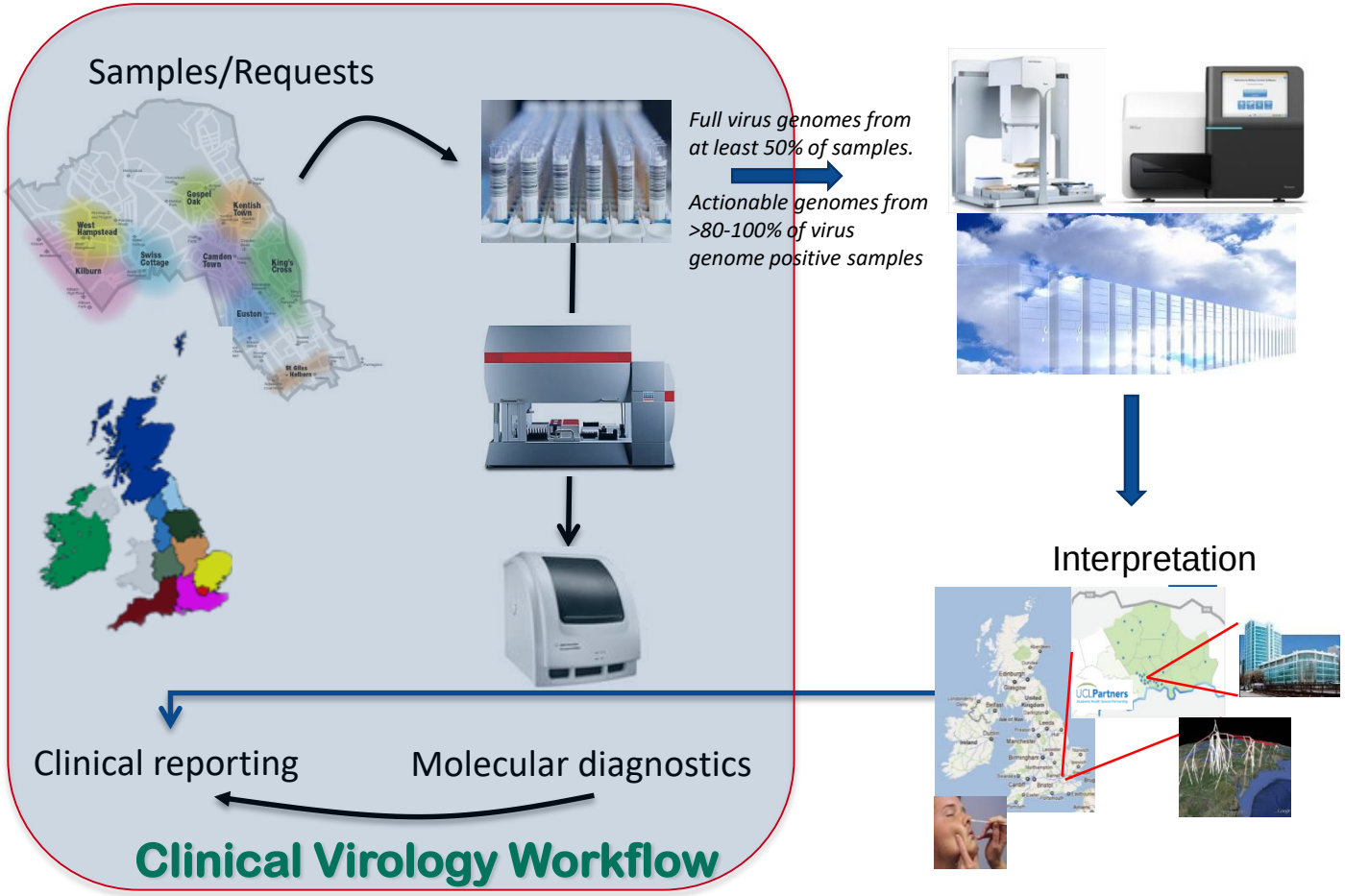
Number of seq sampling since the start of the outbreak in

NRC should provide otocol allowing the set-up of real-time new variants' su illance by routine clinical laboratories

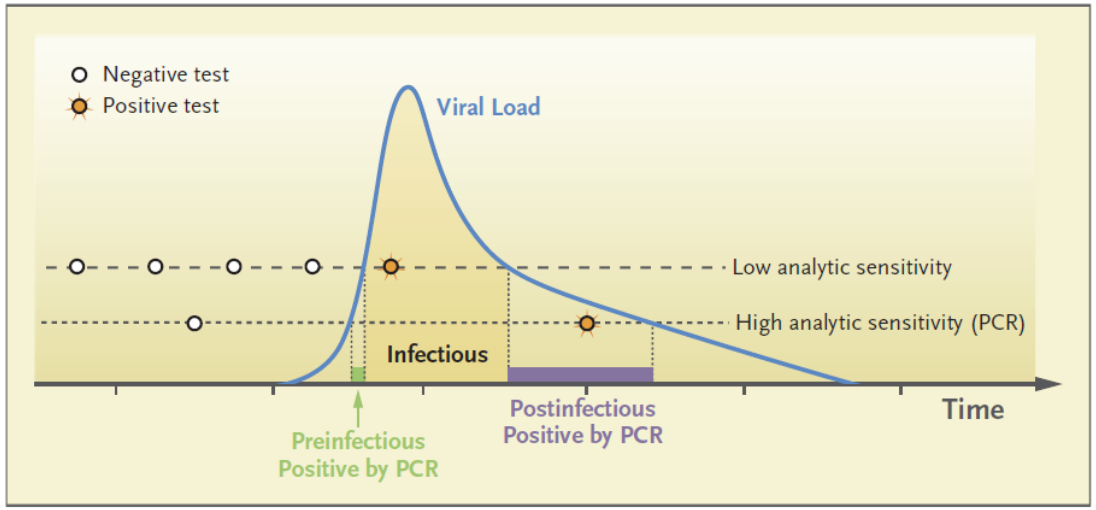
Performing a reflex PCR on all (or a significant proportion) of positive samples would allow to rapidly detect and subsequently contain community clusters of transmission related to such VOCs. Considering the financially advantageous conditions currently offered to clinical laboratories for diagnostic PCR tests, this reflex PCR complementing a positive result could eventually be offered at no (or reduced) cost for the public health budget during a limited period of time. The implementation of such PCR should be considered as necessary as long as VOCs harbouring the S:E484K mutation remain a minority of the circulating strains and as long as the health inspectors can handle the workload related to the specific interventions required.

# Genomic surveillance of SARS-CoV-2 in Belgium

## ICONIC virus genomes to clinical/epidemiological workflow



# What next?
# Implementation of integrative diagnostic approach allowing lockdown exit strategy




**High-Frequency Testing with Low Analytic Sensitivity versus Low-Frequency Testing with High Analytic Sensitivity.**

A person's infection trajectory (blue line) is shown in the context of two surveillance regimens (circles) with different analytic sensitivity. The low-analytic-sensitivity assay is administered frequently and the high-analytic-sensitivity assay infrequently. Both testing regimens detect the infection (orange circles), but only the high-frequency test detects it during the transmission window (shading), in spite of its lower analytic sensitivity, which makes it a more effective filter. The window during which polymerase chain reaction (PCR) detects infections before infectivity (green) is short, whereas the corresponding postinfectious but PCR-detectable window (purple) is long.

**Rethinking Covid-19 Test Sensitivity — A Strategy for Containment**
Mina MJ, N Engl J Med. 2020. doi: 10.1056/NEJMp2025631

- We have to shift our attention from a narrow focus on the sole analytical performances of the diagnostic tools available to an integrated approach taking into account (i) practical consideration such as time- result, field ease-of-use, availability of reagents (ii) target populations (iii) intended use of produced results, and (iv) kinetic of the epidemic.

- The ability to directly connect laboratory-produced data (for example, viral genomic data) and records from the laboratory information system to national public health surveillance systems or international networks will be crucial in the control of COVID-19

**Considerations for diagnostic COVID-19 tests**
Vandenberg O. Nat Rev Microbiol. 2021. doi: 10.1038/s41579-020-00461-z

# Conclusion

- The centralization of tests at the start of the epidemic (as in other European countries) contributed to delays in the diagnosis and therefore definitely to the spread of the epidemic.
- A same error was made for sequencing by limiting the reimbursement of the test to NRC only. Since mid-December 2020, all platforms bis performing sequencing are reimbursed by social security. Such reimbursement should be extended to the clinical laboratory for sequencing related to their clinical activities only.
- The implementation of the first federal diagnostic platforms would have been improved if it had been carried out in close collaboration with clinical laboratories. This error was corrected when creating the platforms bis.
- According my field experience, the prevention of a third wave will go through the massive use of molecular and antigenic diagnostic tests by adapting their use according to the target population and the purpose of the analysis (clinical care, prevention, screening, ...)
- Finally, the complexity of the different structures involved in the management of the crisis does not allow us to take advantage of all the skills existing in our territory.

# Acknowledgements


- LHUB-ULB and the Brussels University Hospital Network

- I would like to express my thanks to all the individuals involved in fight against COVID-19.

- We are also grateful to Sciensano's partners for their strong support and the open discussion we hade since the start of the pandemic.


- Additional request for information may be sent to the following e-mail address: olivier.vandenberg@lhub-ulb.be

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# Thank You

Any Questions ?