RECOMMANDATIONS POUR L'UTILISATION DES TESTS PCR MULTIPLEX POUR LA DETECTION SIMULTANEE DU SARS-COV-2 ET D'AUTRES INFECTIONS RESPIRATOIRES - MISE A JOUR SEPTEMBRE 2021

RAG sous-groupe testing – 6 septembre 2021, validé par le RMG 9 septembre 2021

Note : Les recommandations actuelles sont susceptibles d'être modifiées en fonction de nouvelles informations et/ou de l'évolution de l'épidémie.

Principales recommandations:

- Que les autorités compétentes prennent une décision dans les meilleurs délais concernant le remboursement des tests PCR pour les infections respiratoires autres que COVID-19 (y compris les tests multiplex).
- Que les tests multiplex qui détectent simultanément le SARS-CoV-2 et d'autres agents pathogènes respiratoires sont utiles dans les périodes où plusieurs agents pathogènes respiratoires sont en circulation, comme lors d'une épidémie simultanée de COVID-19 et de grippe.
- L'utilisation de ce type de test multiplex est prioritairement destinée aux patients souffrant ou risquant de souffrir d'une infection respiratoire aiguë (IRA) grave. Il s'agit principalement de patients en hôpital (hospitalisés ou aux urgences) présentant une IRA grave ou à risque d'IRA grave (tels que les patients immunodéprimés, les patients avec comorbidités graves et les personnes âgées).
- La deuxième priorité concerne les résidents des maison de repos et des soins atteints d'une IRA, en particulier dans un contexte de clusters.
- L'utilisation de tests multiplex en médecine générale n'est actuellement pas recommandée, mais peut être envisagée à long terme.
- Les tests multiplex ne doivent être utilisés que si le diagnostic différentiel conduit effectivement à une meilleure approche, telle que des mesures d'isolement appropriées, l'évitement d'investigations et de traitements supplémentaires et inutiles, ou une prise en charge clinique appropriée.

Les personnes suivantes ont participé à cet avis :

Emmanuel André (KU Leuven-NRC); Bénédicte Delaere (CHU-UCL Namur); Olivier Denis (CHU-UCL Namur); Achille Djena (AVIQ); Yves Lafort (Sciensano); Tinne Lernout (Sciensano); Elizaveta Padalko (UZGent); Patrick Smits (AZG); Ann Van den Bruel (KU Leuven); Steven Van Gucht (Sciensano); Pieter Vermeersch (UZ-Leuven); Clotilde Visée (AVIQ).

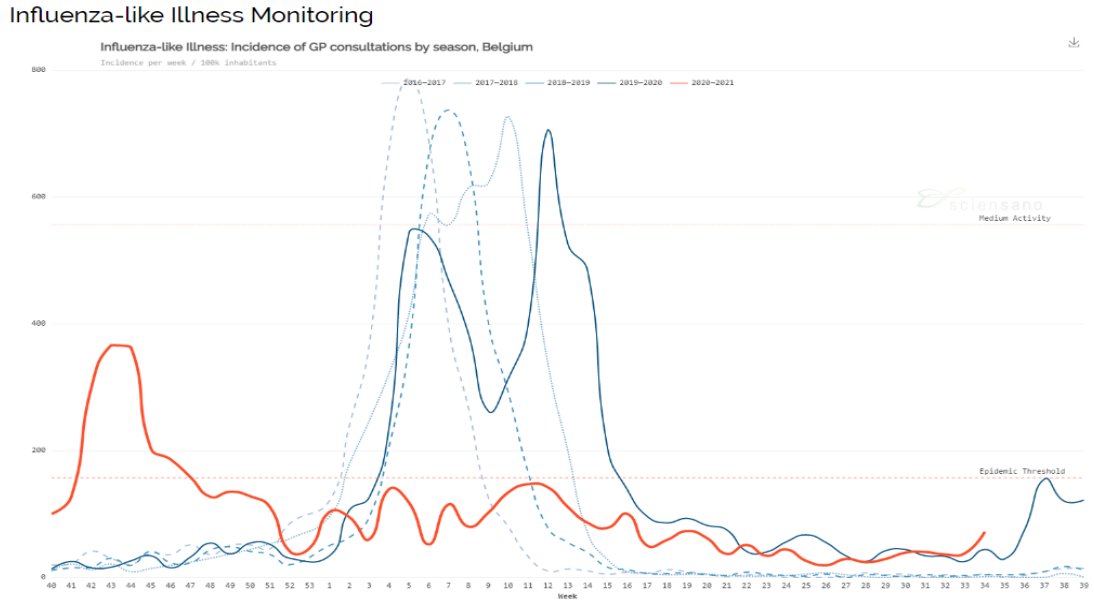
CONTEXT

With the current relaxations of measures, it is expected that in the next autumn and winter the circulation of seasonal respiratory viruses other than SARS-CoV-2, such as RSV or influenza, will increase. An advice was therefore requested with regards to the use of multiplex PCR for co-detection of SARS-CoV-2 and other respiratory pathogens.

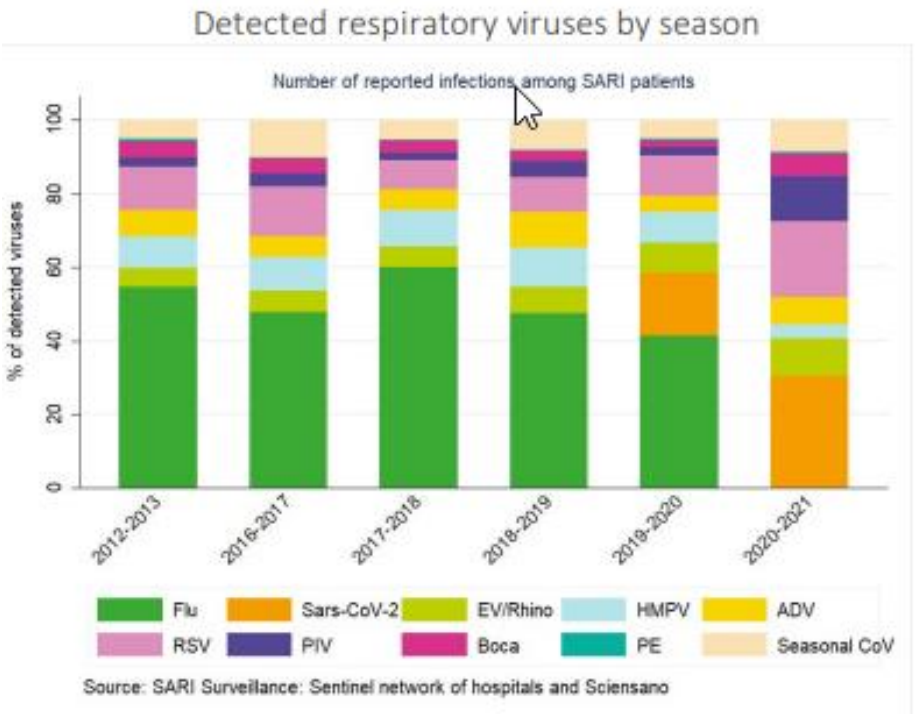
An advice on the use of multiplex PCR was given in September 2020[1] and re-endorsed in December 2020[2]. The recommendations are listed in annex. In short, the use of multiplex assays was only recommended if there would be effectively a seasonal influenza epidemic, and only in patients attending hospitals. Since there was no substantial influenza epidemic in the 2020-2021 season, the use of multiplex PCR was never recommended (except in a surveillance context).

INFLUENZA LIKE ILLNESSES IN BELGIUM

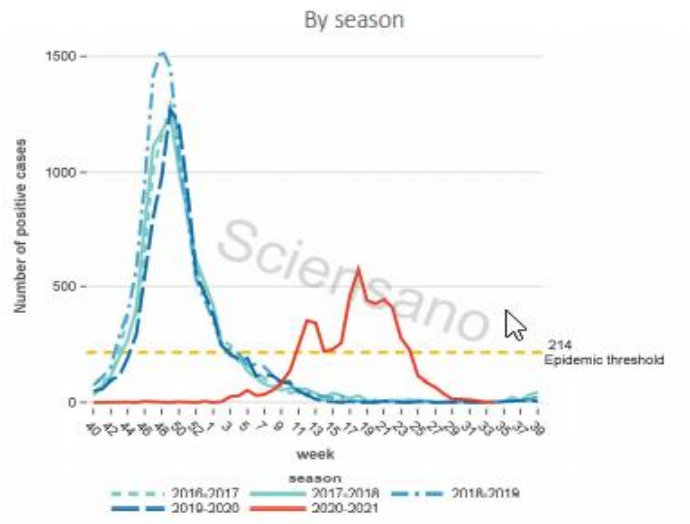
The figure below presents the trends in influenza like illnesses (ILI) in past years in Belgium[3]. The period with the highest incidence of ILI consultations in general practices, in a normal year, is from January to April. In the period April 2020-currently, the ILI trend is mainly determined by COVID-19 infections with the peaks corresponding with the COVID-19 waves (red line).

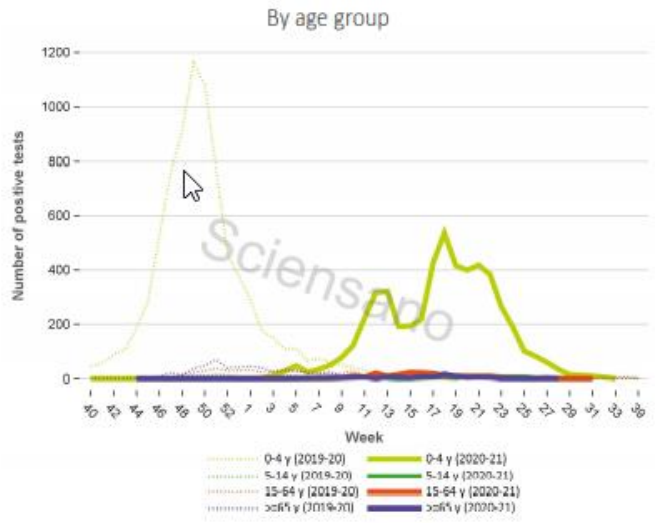


[1] See: 20200909_Advice RAG_test strategy_update September_NL.pdf (sciensano.be)
[2] See: 20201214_Advice_RAG_test strategy_update December_Nl.pdf (sciensano.be) or 20201214_Advice_RAG_test strategy_update December_FR.pdf (sciensano.be)
[3] Source: Influenza (wiv-isp.be)



The second figure shows the relative proportion of pathogens detected in the ILI surveillance. While there were few influenza cases detected in the 2020-2021 season, the number of RSV infections was substantial. This is mainly due to a surge among children aged 0-4 years in the period March-April 2021, during which the epidemic threshold was surpassed (see graphs below) This was unexpected because the RSV season in Belgium is normally in October-February.





DISCUSSION

- In the past winter season (2020-2021) there was only a very limited influenza epidemic in Belgium, and elsewhere in the world. The main reason is believed to be the non-pharmaceutical measures (NPI) that also impacted on the transmissibility of influenza and other respiratory infections.
- With the relaxation of measures it is expected that next winter there will be an influenza epidemic. In some countries, including Belgium, there have already been surges of other respiratory infections (for example RSV). Surges of RSV outside the normal seasonal epidemic are however not that uncommon.
- The impact of the influenza epidemic the coming season is uncertain. It might be more severe, because of diminished population immunity and a possible mismatch with current vaccines. On the other hand, some believe that SARS-CoV-2 might interact with other respiratory viruses and reduce the risk of infection, based on lower SARS-CoV-2 infection rates among flu positive cases than among flu negative cases.
- There is some evidence that COVID-19/influenza co-infected patients suffer a more severe disease and have a higher mortality rate.
- Several countries (US, UK, France) developed guidelines for multiplex testing during the influenza season. These guidelines were developed in preparation of the previous season. They have not yet been updated and it is therefore assumed they also apply to the upcoming season.
- All these countries recommend testing for both COVID-19 and influenza in hospitalized ARI patients and in nursing home residents with ARI. Some countries also recommend it in primary health care (using rapid point of care tests), but only if it changes clinical management or influenza infection control (for example returning nursing home residents). France also recommends multiplex tests (including RSV) in infants or children with a severe form of disease and fulfilling COVID-19 case definition criteria.
- The arguments listed for multiplex testing are:
    - to quickly implement isolation measures to avoid nosocomial transmission and putting influenza patients in isolation with SARS-CoV-2 positive patients risking an influenza/COVID-19 co-infection;
    - to make the right diagnosis by avoiding unnecessary investigations and antibiotic therapy;
    - to timely treat patients (within 48 hours of the onset of symptoms) presenting a severe form of influenza with the antiviral Tamiflu® (oseltamivir).
- However, all these countries commonly use Tamiflu® for the treatment of influenza patients with or at risk for severe disease, while this is not the case in Belgium. Nevertheless, the usefulness of multiplex testing is more than only for guiding clinical treatment. It also helps to guide the broader patient management, for example for infection control measures, avoid unnecessary tests and treatments… (as listed in the arguments above).
- PCR tests for respiratory infections other than COVID-19 (including influenza and RSV) are currently not reimbursed in Belgium. The use and reimbursement of multiplex and single PCR

tests for respiratory pathogens has been discussed for several years now and the Microbiology Working Group of the Commission Clinical Biology has already developed several proposals. The current recommendations of the RAG Testing with regards to multiplex tests that include SARS-CoV-2 have therefore to be seen in this context and are conditional on a rapid decision on the financing and reimbursement of this type of tests. This decision is urgent because it is unknown when influenza, or other respiratory pathogens, will start to circulate and the labs need time to prepare. ~~The strategy for the use of multiplex tests for respiratory pathogens should be aligned with the strategy for the use of individual tests for specific respiratory pathogens, and it only makes sense to recommend multiplex testing if testing for these pathogens (outside a COVID-19 epidemic) is also recommended.~~

- While it is true that multiplex testing is only useful when several pathogens are co-circulating, it is often difficult to precisely delimit these periods. There should therefore be some flexibility on when these tests can be used.

- Multiplex testing is most necessary in populations that are vulnerable to severe forms of acute respiratory infections, such as immunocompromised patients or the elderly. The highest priority is in hospitals, in patients with severe disease. If the availability of funds for reimbursement is sufficient, the indications can be expanded to other hospitalized patients, patients at the emergency department and nursing home residents. For the latter, it has to be clear what the purpose of the differential diagnosis is. For example, if it is purely for infection control measures (putting people with influenza in isolation), the negative impact of isolation has to be weighed against the advantage. In a first phase, multiplex testing in nursing home residents could be limited to when there is a cluster of ARIs.

- On the long term the use of multiplex testing in ambulatory care (general practitioners), using PoC tests, can be considered, but for the moment the first priority is to ensure its availability at the hospital level.

RECOMMENDATIONS

- The RAG Testing strongly recommends the responsible authorities to urgently make a decision on the reimbursement of PCR tests for respiratory infections other than COVID-19 (including multiplex PCR tests)

- The first priority for the use of multiplex tests that co-detect SARS-CoV-2 and other respiratory pathogens is in patients at the hospital with or at increased risk for severe COVID-19 and/or severe disease by other respiratory infections. These include patients presenting with severe acute respiratory infection (ARI) and patients at risk for severe ARI, such as immuno-compromised patients, patients with severe comorbidities (pulmonary, cardiac…) and the elderly. Both hospitalized in-patients and out-patients at the emergency department are considered.

- The second priority are nursing home residents with ARI, in particular in a context of a cluster.

- Multiplex testing at primary health care services (general practitioners), using point-of-care rapid PCR tests, is currently not recommended, but might be considered in the future.

- The RAG Testing maintains its recommendation to limit the use of SARS-CoV-2/other respiratory pathogen multiplex test to periods during which both SARS-CoV-2 and other

respiratory pathogens are simultaneously and strongly circulating, such as during the influenza season. The RAG Testing does however not establish fixed criteria for when this is effectively so, and a certain flexibility is necessary.

- Multiplex tests should only be used if the differential diagnosis effectively results in a different management of the patient, such as different isolation measures, avoidance of further investigations and unnecessary therapies, or a different clinical management.

INTERNATIONAL RECOMMENDATIONS

WHO did not publish any new guidance since its policy brief on readiness for influenza during the COVID-19 pandemic of November 2020. It recommends to test patients with severe or complicated disease or those with risk factors (regardless of severity) for influenza using a rapid molecular assay when results can be made available within 24 hours preferably. Awaiting test results should not delay empiric treatment, which can be modified subsequently, according to test results. The longer the time lag between sampling and test results, the less the test will benefit clinical management. Empiric treatment without laboratory diagnosis could lead to expanded use of oseltamivir (Tamiflu®) and could contribute to overuse and the development of resistance.

Also **CDC**'s recommendations on influenza date from last year (October 2020 - Testing Guidance for Clinicians When SARS-CoV-2 and Influenza Viruses are Co-circulating). It provides guidelines for patients at the out-patient or emergency department, requiring hospitalization and not-requiring hospitalization, and for nursing home residents.

Patients not requiring hospitalization are recommended to be tested for SARS-CoV-2 (with RT-PCR or rapid Ag test) and

- OR to be tested for influenza, **if results will change clinical management or for infection control decisions** (for example returning nursing home residents). The preferred test is a rapid NAAT or, if not available on site, a rapid influenza antigen assay. (If available, multiplex NAAT for SARS-CoV-2, influenza A and B viruses can be performed on-site, or at an offsite clinical laboratory.)
- OR prescribe empiric antiviral treatment as soon as possible without influenza testing, based on clinical diagnosis, for patients of any age with progressive disease of any duration, and for children and adults at high risk for influenza complications.

Patients requiring hospitalization are recommended to be **tested for SARS-CoV-2 and for influenza**. Testing can be done by Multiplex NAAT influenza A/B/SARS-CoV-2; or if not available, by a separate SARS-CoV-2 NAAT and an influenza NAAT. A rapid influenza antigen detection assay is not recommended for hospitalized patients due to low sensitivities.

Nursing home residents with acute respiratory illness symptoms are recommended to be tested both for SARS-CoV-2 and influenza, applying the same recommendations as for non-hospitalized patients (see above).

In the **United Kingdom**, the latest guidance from the National Institute of Health (NIH) with regards to influenza also dates from October 2020. When influenza viruses and SARS-CoV-2 are co-circulating, it recommends testing for both viruses in all hospitalized patients with acute respiratory illness. In outpatients it is only recommended if the results will change clinical

management of the patient. Testing for other pathogens should be considered depending on clinical circumstances, especially in patients with influenza in whom bacterial superinfection is a well-recognized complication.

A report of the British Academy of Medical Sciences from July 2021 on the future of the response to the COVID-19 epidemic during the winter 2021-2022, provides some background and recommendations with regards to the upcoming influenza season, and other seasonal respiratory infections.

The council is concerned that both the influenza and RSV epidemics might be different from those in previous seasons. The low levels of influenza activity over winter 2020/21 and the mild influenza and RSV season in 2019/20 might have led to a diminished population immunity. Higher infection levels might in particular be expected in younger age groups that were never exposed. There is also an increased likelihood that there will be influenza vaccine mismatch this winter, which could result in more infections and disease. They project that in a worst-case scenario an influenza and a RSV epidemic in the UK this winter could be between 1.5 and 2.2 times the magnitude of a 'normal' year (without measures to reduce transmission). This could result in between a 25% and 65% increase in RSV cases in children under 5 years old, and between 30%-100% increase in the youngest infants. In addition, the RSV epidemic could start sooner than usual.

The council suggests that now that community testing for COVID-19 is common, adding influenza to the tests could potentially reduce pressure on secondary care, particularly if targeted at older people where antiviral prescription is likely to be most beneficial due to higher risk of admission to hospital. It strongly supports multiplex testing and, if not feasible, the use of point-of-care testing in hospitals, in primary care settings, care homes and in community pharmacies. Testing must be sufficiently rapid to make an influenza diagnosis within 48 hours of symptom onset for antiviral treatment (with oseltamivir-Tamiflu®) to be clinically useful. In addition to optimizing appropriate clinical management, rapid testing would minimize patients of unknown SARS-CoV-2 and influenza status being cohorted together, thereby reducing the risk of nosocomial transmission to patients and staff.

With regards to RSV, the council states that the introduction of multiplex testing (at least for SARS-CoV-2, RSV and influenza) will be important for managing febrile children in the coming winter.

In **France**, the Haut Conseil de la Santé Publique (HCSP) developed guidelines in September 2020. It recommended:

- to prioritize the simultaneous testing of SARS-CoV-2 and influenza (using a multiplex test or two tests in parallel) in people at risk of severe disease AND during periods of influenza co-circulation;
- to simultaneously test for SARS-CoV-2 and influenza in nursing home residents with ARI during periods of influenza virus circulation, to initiate antiretroviral treatment in influenza patients;
- to use multiplex tests, if available, in infants or children with a severe form of febrile and/or respiratory and/or digestive symptoms and that fulfill the criteria for SARS-CoV-2 testing.

Consecutively, the Haute Autorité de Santé (HAS) published recommendations with regards to testing for differentiating between COVID-19 and other respiratory infections during periods of co-

circulation in October 2020. It considered the simultaneous testing for COVID-19 and influenza important in the following situations:

- hospitalized patients with symptoms of respiratory infection consistent with an influenza and/or COVID-19 etiology, and this because:
    - to quickly implement isolation measures for influenza patients to avoid nosocomial transmission, but also to avoid putting these patients in isolation with SARS-CoV-2 positive patients risking an influenza/COVID-19 co-infection;
    - to make the right diagnosis by avoiding unnecessary investigations and antibiotic therapy;
    - to treat patients presenting a severe form of influenza with the antiviral Tamiflu®, which must be started rapidly, within 48 hours of the onset of symptoms;
- nursing home residents with symptoms of respiratory infection consistent with an influenza and/or COVID-19 etiology, for the same reasons;
  In these two indications a PCR test is recommended
- children with severe symptoms in the emergency room to orientate complementary investigations allowing to decrease the rate of hospital admission to hospital;
- symptomatic children in first-line consultations to optimize diagnostic and therapeutic management in particular by decreasing the prescription of antibiotics in case of positive test for influenza
  in these two pediatric indications, rapid antigen tests and/or rapid PCR tests, performed on nasopharyngeal samples, are recommended

LITERATURE BACKGROUND

Low rates of co-infections

Several studies have documented low rates of COVID-19/influenza co-infections during the 2020-2021 flu seasons.

Poole et al. assessed the impact of SARS-CoV-2 in the prevalence of respiratory viruses in hospitalized patients (1). They compared samples from March-May 2020 with samples from the same period in previous years. Before 2020, non-SARS-CoV-2 viruses (such as Influenza, rhinovirus, RSV, seasonal coronaviruses or parainfluenza virus) were detected in 54 % of patients. In 2020 non-SARS-CoV-2 viruses were present in 4,1 % of the samples while 38 % of samples were positive for SARS-CoV-2. The emergence of SARS-CoV-2 was therefore associated with reductions in the circulation of seasonal respiratory viruses.

Reduction in the circulation of other seasonal respiratory viruses during the first peak of the epidemic was also observed in several regions worldwide (2–4). An early Italian study however did not see different trends for other respiratory viruses in March 2020 compared to the same period in previous years (5).

Co-infections of SARS-CoV-2 and other respiratory viruses have been described in several reports, the extent of co-infections is variable. In the study from Leuzinger et al. co-infection was shown to occur in 1,8 % of the samples (6), Poole et al. found co-infections of SARS-CoV-2 and other respiratory virus in 1 % of the samples (1). Also other studies found low levels of coinfection

with other respiratory viruses (7). Some studies observed more extended cases of co-infections with bacterial pathogens (8).

Haddadin et al. assessed the frequency of RSV and influenza ARI in children, before and during the COVID-19 pandemic in a cohort of 25,415 children (8). In 2020, they noted a decrease in eligible and enrolled ARI subjects after community mitigation measures were introduced, with no RSV or influenza detection in 4/5-4/30/2020. Compared to 2016-2019, there was an average of 10.6 fewer eligible ARI cases/week per site and 63.9% and 45.8% lower odds of testing positive for RSV and influenza, respectively, during the 2020 community mitigation period.

Competitive effect between SARS-CoV-2 and other respiratory viruses

The low rate of coinfections is mostly attributed to the measures taken to fight COVID-19, such as social distancing and lock-down, that had also an effect on the spread of other respiratory pathogens. Another hypothesis, however, points at interactions and interferences between different viruses. This has been shown for other respiratory viruses (9).

In an analysis of the English national surveillance systems data by Stowe et al. the risk of testing positive for SARS-CoV-2 was 58% lower among flu positive cases than among flu negative cases. This is consistent with the findings by Nowak et al. (10) Amongst patients who tested positive for SARS-CoV-2 concurrent infection was found in less than 3%, while coinfection was found in 13% of patients who tested negative for SARS-CoV-2. Additionally, in patients who tested negative for SARS-CoV-2, the most common respiratory virus co-infections were those commonly seen circulating in the community including rhinovirus/enterovirus, influenza viruses and coronavirus NL63, whereas non-SARS-CoV-2 coronaviridae were the most common concurrent respiratory viruses found in SARS-CoV-2 –positive patients.

Disease severity in co-infected patients

Studies on disease severity in patients co-infected with SARS-CoV-2 and influenza are scarce (greatly because the low rate of coinfections till now). The study by Stowes et al. (see above) found, however, that COVID-19 patients co-infected with influenza had a 2.3 times greater risk of death than non-co-infected patients (11). A study in 32 hospitalized pediatric COVID-19 patients in Brazil, of which 6 co-infected with RSV, found that co-infected patients had a significantly longer length of stay, but there were no differences regarding need for intensive care, mechanical ventilation or mortality rates (12). Simultaneous or sequential coinfection by SARS-CoV-2 and a H1N1 virus caused also more severe disease than mono-infection by either virus in hamsters (13).

Projections for future influenza and RSV epidemics

A modelling study by Baker et al. projected that, due to increased susceptibility substantial outbreaks of RSV may occur in future years in the US, with peak outbreaks likely occurring in the winter of 2021-2022 (14). Results for influenza broadly echo this picture, but are more uncertain. They also state that future outbreaks are likely dependent on the transmissibility and evolutionary dynamics of circulating strains.

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ANNEX: INDICATIONS ON THE USE OF MULTIPLEX PCR – DECEMBER 2020

- During the seasonal influenza epidemic patients with respiratory symptoms, especially in severe condition, can be tested with a multiplex PCR panel in order to guide therapeutic care and support.
- The use of multiplex assays is only recommended if there is evidence of a seasonal influenza epidemic, based on the surveillance data of influenza-like illnesses in Belgium or neighboring countries.
- A multiplex assay is only indicated in patients attending hospitals, both hospitalized in-patients and out-patients at the emergency department. Patients in ambulatory care outside a hospital setting (such as in general practice) should only be tested for SARS-CoV-2.
- Patients with respiratory symptoms without severe clinical condition should be tested with a multiplex PCR mini panel (SARS-CoV2/ Influenza A and B, or SARS-CoV2/ Influenza A and B/ RSV).
- Patients with respiratory symptoms and a severe clinical condition can be tested with a multiplex PCR maxi panel (detection of a broad range of pathogens), if available.
- Multiplex assays should be done on specimens that ensure a high sensitivity, such as nasopharyngeal swabs, nose/throat swabs, tracheal aspirate or broncheo-alveolar lavage fluid (BAL); and not on specimens with lower sensitivity, such as salivary samples.