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Donia Bouzid

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Stratégies de diagnostic rapide des infections respiratoires virales aux urgences

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Soutenue le 28 mai 2021

Thèse de doctorat de Santé Publique,
Spécialité Épidémiologie Clinique
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Stratégies de diagnostic rapide aux urgences des infections respiratoires virales

Les infections respiratoires hautes et basses constituent un motif fréquent de recours aux soins. Parmi les suspicions d'infections respiratoires basses aux urgences, les virus respiratoires sont retrouvés dans 30 à 50% des cas. Leur diagnostic précis et rapide est nécessaire au bon usage des anti-infectieux, au recours à l'hospitalisation, à la gestion du flux de patients et à l'instauration des mesures de précaution nécessaires. Nous avons évalué l'impact de l'implémentation d'une PCR multiplex permettant un diagnostic syndromique rapide et délocalisé dans un service d'accueil des urgences des virus responsables d'infections respiratoires. Dans un premier temps, nous avons réalisé une revue narrative des tests microbiologiques disponibles puis nous avons:

- Étudié l'impact du délai de réponse du laboratoire de virologie centralisé (médiane 18h) sur les stratégies de placement en chambre seule des patients présentant une infection par des virus influenza,
- Mené une étude de faisabilité de l'implémentation d'une technique de PCR syndromique rapide délocalisée aux urgences,
- Évalué prospectivement l'impact de la réponse virologique rapide sur la prise en charge des patients suspects d'infections respiratoires basses à l'aide d'une essai clinique contrôlé,
- Étudié, au début de la pandémie de SARS-CoV-2, les caractéristiques cliniques et biologiques qui permettaient de distinguer les patients infectés par le SARS-CoV-2 ou un autre virus respiratoire comme les virus influenza, le VRS ou le rhinovirus.

Nous avons ainsi montré :

- que le long délai de rendu du laboratoire centralisé ne permettait pas une prise en compte efficace du résultat de PCR pour le placement des patients grippés en chambre seule,
- que le diagnostic viral délocalisé aux urgences est possible et permet plus d'hospitalisation en chambre seule pour les patients influenza positif au cours de l'étude randomisée (74% vs 50%), mais pas trouvé de bénéfice du diagnostic délocalisé sur la durée de l'antibiothérapie ou de l'hospitalisation.
- que la fièvre, l'âge, le sexe masculin et l'absence d'expectoration étaient plus fréquemment associés au diagnostic d'un SARS-CoV-2 que d'un autre virus respiratoire et que la co-infection d'un SARS-CoV-2 avec un autre virus respiratoire n'était pas associée à un pronostic plus sévère.

Il paraît aujourd'hui nécessaire d'intégrer la mPCR dans une stratégie plus large, incluant scanner et marqueurs d'inflammation, pour une prise en charge optimale aux urgences et impacter la consommation d'antibiotiques et les durées de séjours.

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Introduction

Préambule

Les pneumonies aiguës communautaires sont la première cause infectieuse de décès dans le monde et la troisième cause de décès, toutes causes confondues. La pandémie actuelle de SARS-CoV-2 illustre particulièrement aujourd'hui l'intérêt du diagnostic rapide des infections respiratoires virales et l'importance d'y déployer les moyens nécessaires. À défaut de disposer d'un arsenal thérapeutique efficace pour ces infections virales permettant un bénéfice individuel, un diagnostic rapide permet d'instaurer, au plus vite, les précautions gouttelettes et ainsi d'éviter les épidémies nosocomiales grevées d'une importante morbi-mortalité. Les infections respiratoires virales partagent en général le tableau clinique du syndrome grippal ou « *influenza like illness* », les signes sont peu spécifiques et orientent mal le médecin vers l'étiologie virale, bactérienne ou parfois de pathologies non-infectieuses. La prise en charge de ces infections virales, classiquement hivernales représente un vrai défi diagnostique, notamment pour tout médecin car même si les nouvelles méthodes de diagnostic moléculaire (PCR multiplex) sont performantes, contrairement aux tests rapides immunochromatiques qui ont des sensibilités limitées (40-70%), leur disponibilité et leur délai de rendu de résultat peuvent être relativement longs et donc inadaptés à la gestion du flux au sein d'un service d'accueil des urgences. De ce fait, les décisions de placement en chambre seule ou d'instauration d'un traitement doivent en majorité être prises avant la connaissance du résultat de la PCR, ce qui engendre des inadéquations.

Pour répondre à cette problématique, l'implémentation de techniques de PCR multiplex au lit du malade « point of care » pourrait permettre un diagnostic rapide et avoir un impact sur les précautions gouttelettes des patients (placement en chambre seule) et sur la prescription d'antibiotiques. D'un autre côté, cette approche se heurte aux coûts des techniques ainsi que des problèmes de faisabilité de la délocalisation aux urgences et de l'accompagnement du laboratoire, la biologie délocalisée étant souvent plus coûteuse et chronophage.

Définition des infections respiratoires

Les virus sont responsables d'infections respiratoires hautes comprenant la sphère ORL (angines, pharyngites, laryngites, rhinites et otites) et d'infections respiratoires basses comprenant les bronchites et pneumonies qui sont l'objet de ce travail.

Le tableau clinique associe généralement des signes respiratoires et des signes généraux peu spécifiques. Les signes respiratoires peuvent comprendre : une toux, une dyspnée et souvent une anomalie auscultatoire. Les signes généraux peuvent comprendre : une fièvre ou une hypothermie, des myalgies, des sueurs, des céphalées, une asthénie ou une sensation de malaise. Ces symptômes sont communs à la fois aux virus et aux bactéries et peuvent être à l'origine de ces infections respiratoires basses.

La bronchite aigue est une inflammation des bronches chez un patient n'ayant pas un terrain de bronchopneumopathie chronique et obstructive. Son étiologie est presque toujours virale [1].

La pneumonie aigue est une inflammation aigue du parenchyme pulmonaire, elle peut être d'origine bactérienne ou virale. On distingue les pneumonies communautaires survenues en ville des pneumonies d'origine nosocomiale qui surviennent après 48 heures d'hospitalisation. Ces pneumopathies sont aussi à distinguer des pneumopathies associées aux soins qui surviennent chez des patients hospitalisés ou ayant eu une hospitalisation récente, dialysés chroniques, résidents en maison de retraite, et immunodéprimés [2].

La prise en charge thérapeutique et le pronostic des pneumonies aiguës communautaires et nosocomiales sont différents pour tenir compte des différentes étiologies et typologies de patients [3].

Dans ce travail, nous nous intéresserons uniquement à l'entité des pneumonies aiguës communautaires.

Épidémiologie des pneumonies aiguës communautaires (PAC) :

Les pneumonies aiguës communautaires sont la première cause infectieuse de décès dans le monde et la troisième cause de décès, toutes causes confondues [4].

D'après une large cohorte de patients admis pour une pneumonie aigue à Louisville entre 2014 et 2016, on estime le nombre de patients atteints de pneumonie aigue communautaire à 1,5 millions par an aux États Unis [5]. La mortalité hospitalière est de 6,5%, ce qui correspond à 10 2821 décès annuels aux États-Unis. La mortalité à 30 jours, 6 mois et 1 an était respectivement de 13,0%, 23,4% et 30,6%. Le fardeau économique associé à ces pneumonies aiguës communautaires est par ailleurs conséquent, car supérieur à 17 milliards de dollars par an aux États-Unis.[6] L'incidence annuelle des pneumonies, en France est estimée à 10 cas pour 1000 habitants, soit environ 600 000 cas/an en France, dont 15 % des cas sont hospitalisés [7].

L'incidence globale de la PAC en médecine générale, en Europe, serait comprise entre 1,7 et 11,6 cas pour 1 000 personnes et par an chez les adultes. Dans l'Union Européenne (UE), environ 3 370 000 cas sont attendus chaque année. Les taux d'hospitalisation varient considérablement selon les pays, allant de 20 à 50%, ce qui signifie qu'il y a environ 1 million d'hospitalisations pour PAC par an dans l'UE [8]. Les taux d'hospitalisations ajustés sur l'âge pour pneumonie sont indiqués dans la figure 1.

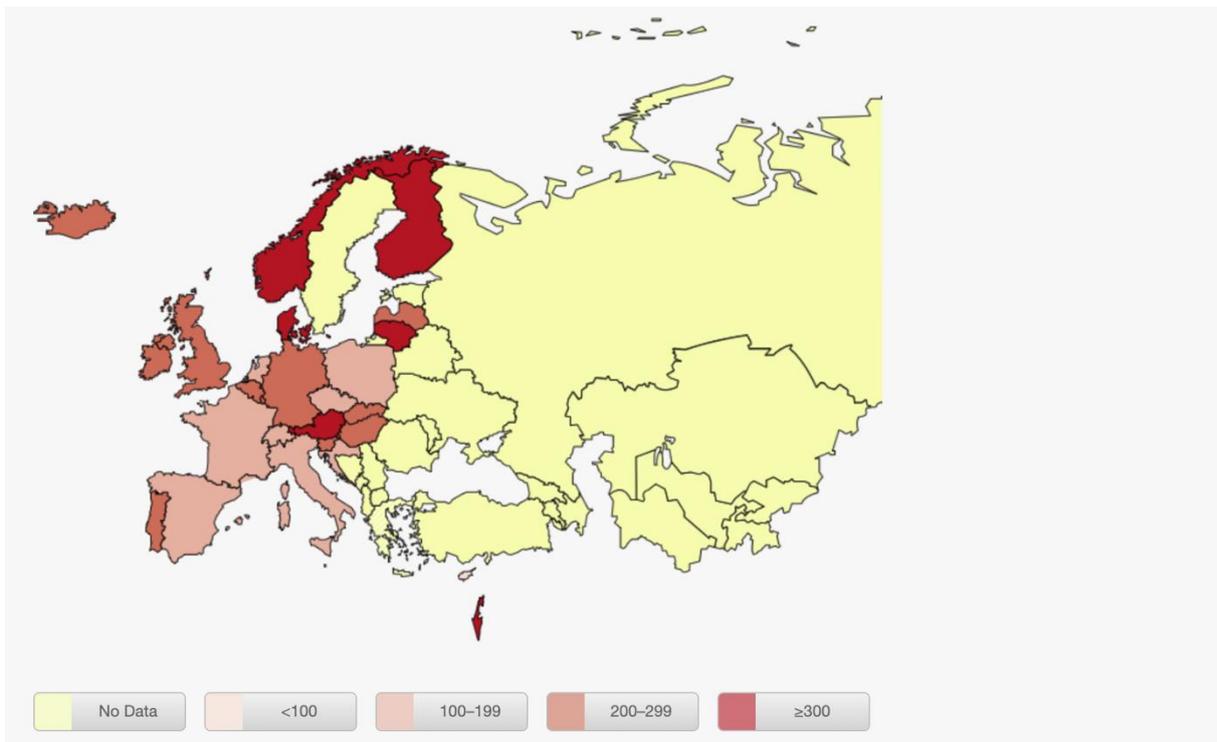


Figure 1. Taux d'hospitalisations pour pneumonie chez l'adulte (taux ajusté sur l'âge pour 100 000 ≥ 15 ans). Données de la base de données sur la morbidité de l'Organisation mondiale de la santé, mise à jour d'octobre 2011, et Eurostat, mise à jour de mars 2012.

L'incidence des PAC augmente avec l'âge [5,9,10]. Une étude américaine rapporte que les hospitalisations annuelles chez les adultes âgés (>64 ans) pour 100 000 habitants pour les années 2007 à 2009 étaient de 1 507 pour la tranche d'âge des 65 à 74 ans, de 2 205 pour les 75 à 84 ans et de 3 851 pour les plus de 85 ans [11]. Cette même étude estimait qu'environ 100 000 adultes mourraient au cours de leur hospitalisation en raison de la PAC. Environ 1 patient sur 10 hospitalisé avec une PAC a nécessité une deuxième hospitalisation en raison d'un nouvel épisode de PAC au cours de la même année.

On observe aussi une saisonnalité dans les admissions pour pneumonies aiguës communautaires avec un pic hivernal, dans les pays de l'hémisphère nord (Figure.2) [12].

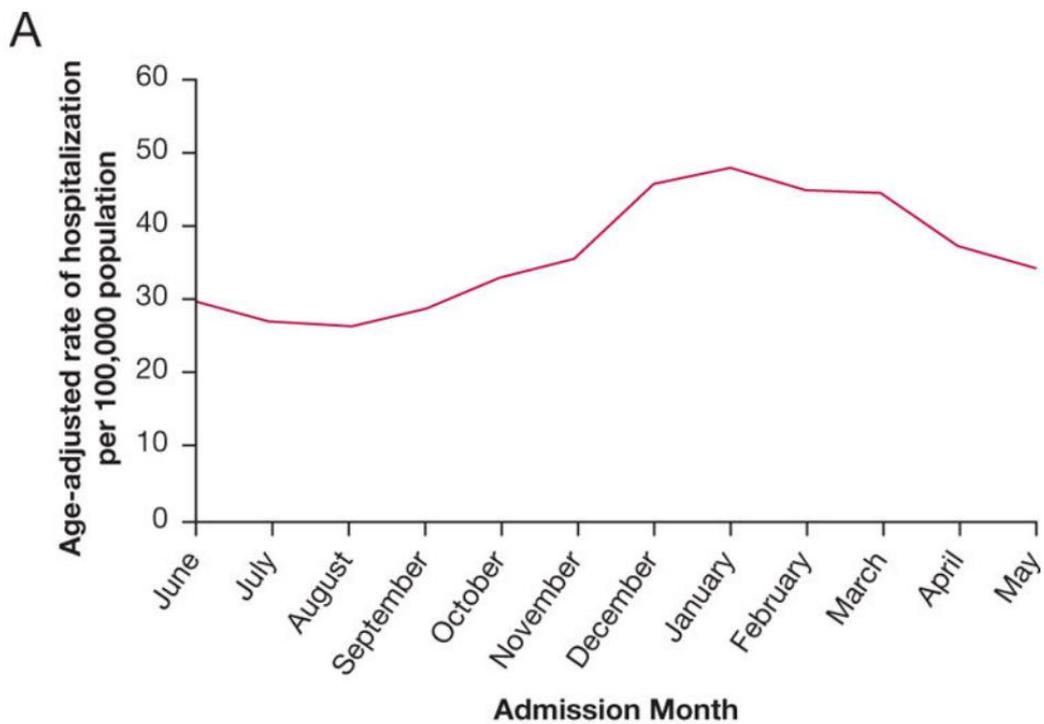


Figure 2. Taux ajusté selon l'âge d'hospitalisations associées à une pneumonie par mois d'admission États Unis 2001-2014, [12]

Agents pathogènes responsables des pneumonies virales

Les virus sont une cause importante de PAC, y compris les virus non influenza qui ont été longtemps considérés comme bénins et ne pouvant pas être à l'origine de présentations sévères nécessitant une hospitalisation [13]. Une étude américaine conduite chez 2 259 adultes admis pour une pneumonie montre que 21% des PAC ont eu besoin d'être pris en charge en unité de soins intensifs, que l'infection n'a été documentée que dans 38% des cas, avec 23% de pneumonies virales, 11% de pneumonies bactériennes, 3 % de co-infections virales et bactériennes et 1% de pneumonies fongiques. Le rhinovirus arrive en tête des pathogènes retrouvés (9%), suivis des virus influenza (6%) puis du *streptococcus pneumoniae* (5%) (Figure 3) [14].

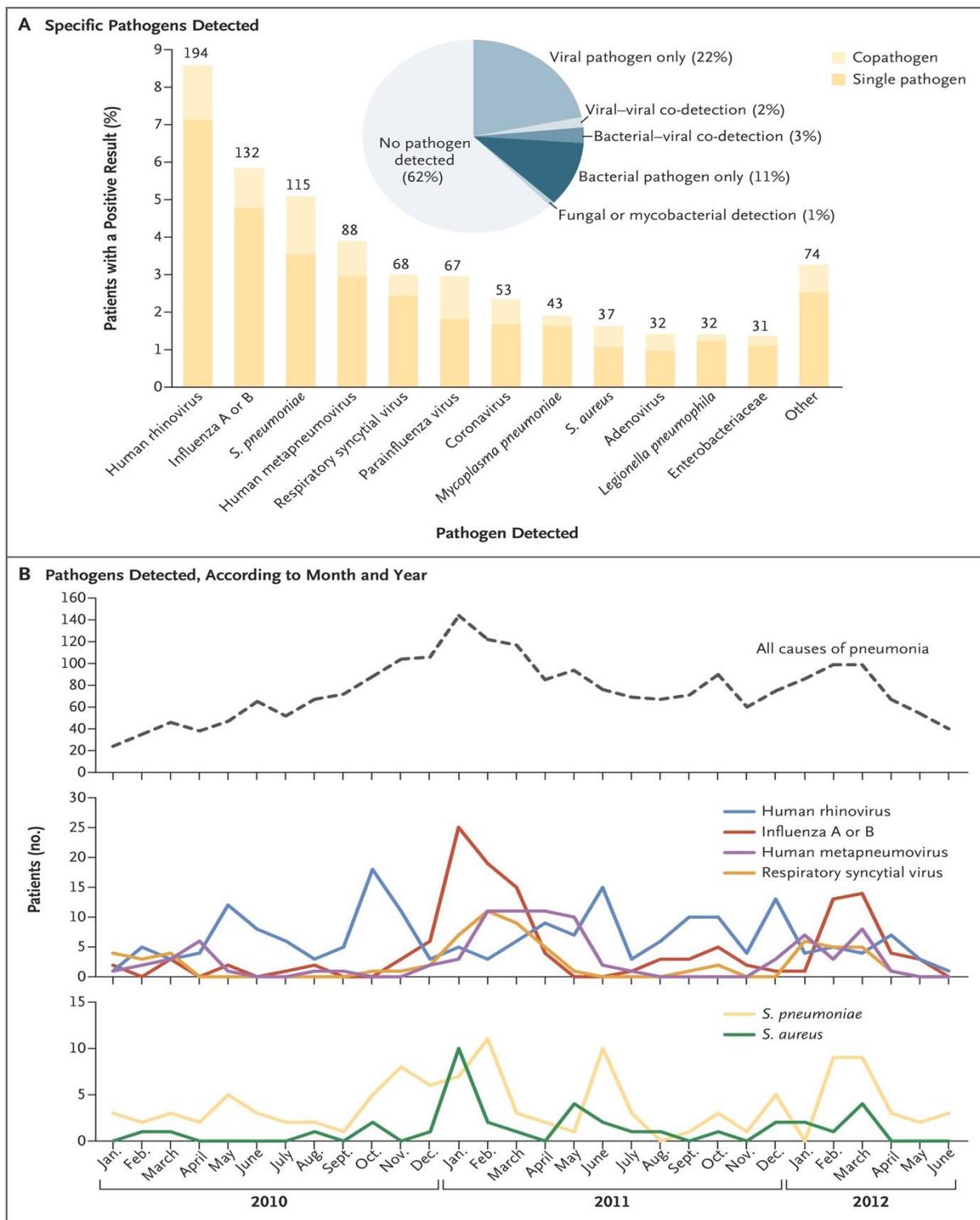


Figure 3 Agents pathogènes détectés chez les adultes américains atteints de pneumonie communautaire nécessitant une hospitalisation, 2010-2012.[14]

Une méta-analyse réalisée sur des études européennes a quant à elle montré une incidence poolée de 22% de pneumopathies virales parmi les pneumonies aiguës communautaires, avec en tête les virus influenza (9%), les rhinovirus (5%) puis les coronavirus (4%) [15].

Une étude anglaise réalisée chez 232 adultes admis pour une pneumonie aiguë a montré la détection d'un pathogène dans 87 % des cas, lors du recours au diagnostic moléculaire par PCR versus 39% de détection de pathogènes, en ayant recours à la technique de culture. Les pneumonies d'origine virale étaient l'ordre de 30% ,avec dans 82% des cas une co-infection bactérienne [16].

Ce qui est intéressant à noter en regardant la figure 3, tirée de l'étude américaine réalisée sur 2 259 patients hospitalisés pour une pneumonie, c'est la saisonnalité des virus respiratoires [14], avec un pic hivernal pour les virus influenza et une circulation plus étalée sur l'année pour les rhinovirus ou les parainfluenza. Ces données sont similaires à celles observées dans notre groupe hospitalier Paris Nord (Figure 4) [17].

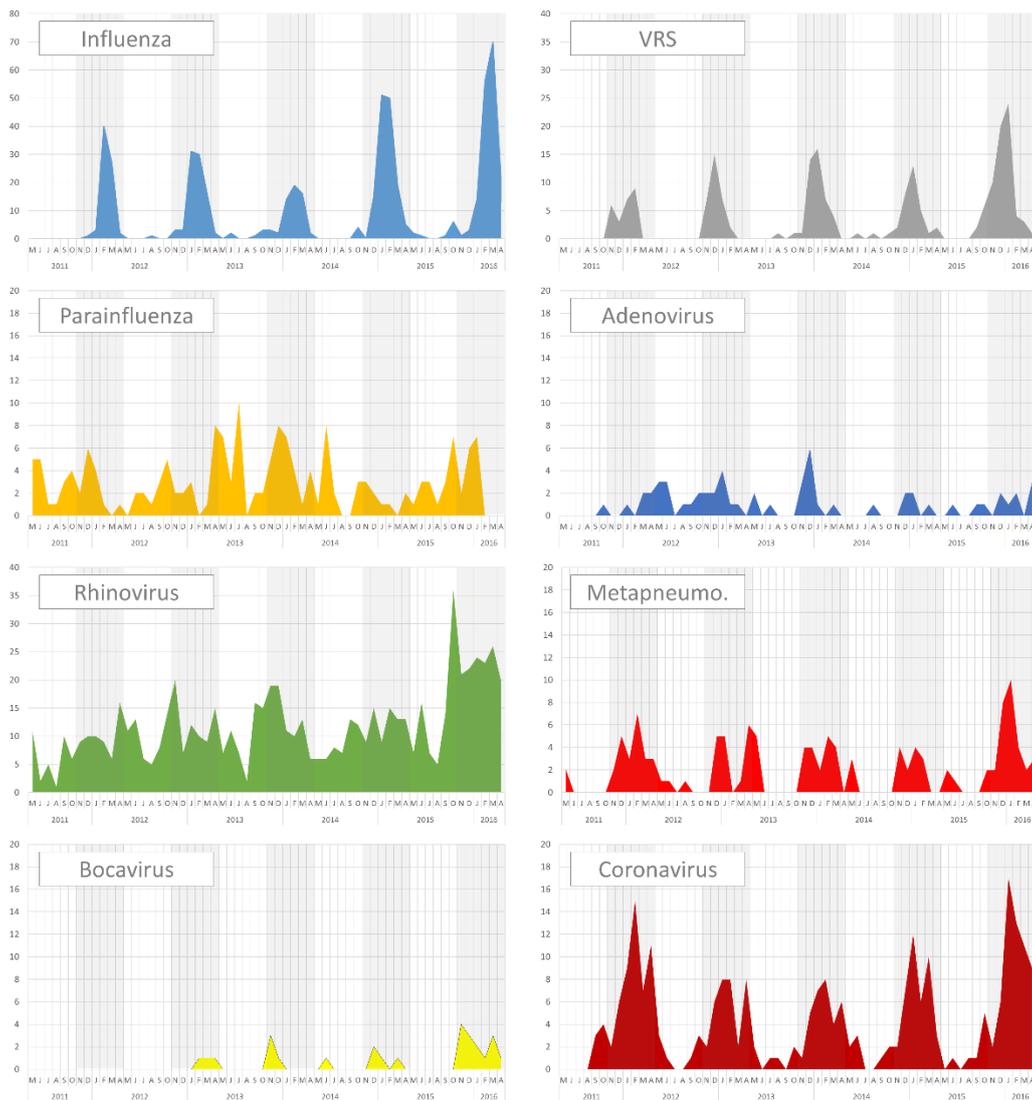


Figure 4 Saisonnalité des virus respiratoires au sein du groupe hospitalier Paris Nord [17].

Techniques de diagnostic virologique pour les virus respiratoires

Les Techniques de diagnostic virologique n'ont pas cessé d'évoluer lors de ces dernières années avec des performances de plus en plus fiables et des délais de rendu de résultats de plus en plus courts. En voici les principales catégories.

Culture virale, immunofluorescence et sérologie :

La culture virale est aujourd'hui uniquement réservée à un usage de recherche au sein de laboratoires très spécialisés. En effet, les résultats de la culture virale peuvent prendre de 3 à 10 jours. La culture nécessite aussi un ensemencement rapide des prélèvements pour conserver le

pouvoir infectieux des virus, nécessite un fort inoculum viral et tous les virus respiratoires ne sont pas cultivables sur les modèles cellulaires usuels. Cependant, la culture virale permet une caractérisation phénotypique approfondie des virus que l'on peut cultiver. Cette technique n'est donc pas adaptée au diagnostic des infections respiratoires virales [18].

En ce qui concerne l'immunofluorescence, le principe repose sur la détection d'un antigène viral au sein des cellules du patient, obtenues par un prélèvement nasopharyngé appuyé, à l'aide d'un microscope à fluorescence. Même si les délais techniques sont très courts, de 2 à 4 h, et donc plus courts que ceux de la culture virale, l'immunofluorescence nécessite un prélèvement de très grande qualité et richesse cellulaire. Ces techniques ont aussi le défaut de nécessiter un temps technique important, d'être réservées aux laboratoires de virologie et de ne pas être disponibles pour tous les virus respiratoires existants.

Enfin les méthodes sérologiques ont peu d'intérêt diagnostique pour les infections virales respiratoires en raison des multiples ré-infections. Elles ne sont utiles que pour des études épidémiologiques.

TROD: tests immunochromatographiques rapides.

Les Tests Rapides d'Orientation Diagnostique (TROD) des virus influenza reposent sur des techniques immunologiques qui peuvent détecter les antigènes nucléoprotéiques des virus influenza A et B dans les échantillons respiratoires. Les TROD ont l'avantage de permettre aux médecins d'obtenir une réponse rapide. En effet le résultat apparaît après quelques minutes (moins de 15 minutes, cf tableau 1) [19]. Cependant, ces tests présentent une sensibilité limitée, qui varie généralement de 50 à 70%. On observe une meilleure sensibilité chez les enfants par rapport aux adultes, ce qui est probablement due à la charge virale plus élevée chez les enfants [20]. Les TROD ont également une sensibilité généralement plus faible pour détecter l'antigène viral des influenza B [20,21].

Ces méthodes ont donc de meilleures performances diagnostiques lorsque les charges virales sont plus élevées. La précision des résultats dépend en grande partie du stade de la maladie et de la qualité du prélèvement. Les médecins ou infirmières doivent effectuer un prélèvement naso-pharyngé de bonne qualité pour maximiser la quantité de particules virales échantillonnées. Les conditions de réalisation, le respect strict des temps de lecture de résultat, de préchauffage ou des volumes précis de certains réactifs, peuvent aussi s'avérer contraignants. L'utilisation de ces tests nécessite donc une formation et une organisation strictes au risque de pertes supplémentaires de fiabilité. Enfin, les résultats négatifs des TROD n'excluent pas

l'infection par les virus testés, principalement influenza, et, si la suspicion clinique est élevée, la CDC recommande de faire un test par RT-PCR pour confirmer le résultat ce qui réduit l'intérêt de leur utilisation dans un contexte d'établissement de soin [22].

These tests provide results in 10-15 minutes and differentiate between influenza A and B				
Manufacturer	Product	Platform/Instrument	Approved Specimens ²	CLIA Waived ³
Abbott	Binax Now Influenza A & B Card 2	DIGIVAL™	NPS, NS direct	Yes
Becton Dickinson & Co.	BD Veritor™ Flu A + B	BD Veritor Reader	NPS, NS direct	Yes
Becton Dickinson & Co.	BD Veritor™ Flu A + B	BD Veritor Plus Analyzer	NPS, NS direct	Yes
Quidel Corp.	Sofia® Influenza A + B FIA	Sofia FIA Analyzer	NS, NPS, NPA, NPW direct, NP, NPA, NPW in VTM	Yes
Quidel Corp.	Sofia® Influenza A + B FIA	Sofia 2 FIA Analyzer	NS, NPS, NPA, NPW direct, NP, NPA, NPW in VTM	Yes
Quidel Corp.	QuickVue® Influenza A + B	N/A	NPS, NS direct	Yes
Princeton BioMeditech Corp.	BioSign® Flu A & B LABSCO Advantage Flu A & B LifeSign LLC Status Flu A & B OraSure QuickFlu Rapid A + B Polymedco Poly stat Flu A & B Sekisui Diagnostics OSOM® ULTRA Flu A & B Meridian BioScience ImmunoCard STAT Flu A&B McKesson Consult Diagnostics Influenza A&B	N/A	NS, NPS direct (waived) NPA, NPW (not waived)	Yes
Becton Dickinson & Co.	BD Veritor™ Flu A + B	BD Veritor Reader	NPW, NA, NPS in VTM	No
Becton Dickinson & Co.	BD Veritor™ Flu A + B	BD Veritor Plus Analyzer	NPW, NA, NPS in VTM	No
Remel/Thermo Fisher	XPECT™ Flu A & B	N/A	Nasal wash	No
Sekisui Diagnostics, LLC	Acucy Influenza A&B Test	The Acucy System	NPS, NS direct	Yes
Sekisui Diagnostics, LLC	OSOM Ultra Plus Flu A&B Test	N/A	NPS, NPA, NPW, NS	Yes
Access Bio, Inc.	CareStart Flu A&B Plus	N/A	NPS	No

1. Available FDA cleared tests as of August 2020. List may not include all available test kits approved by the FDA.

2. Approved respiratory specimens according to manufacturer's package insert.

3. Ref: <http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html> 

Tableau 1 Liste des TROD influenza approuvés par la Food and Drug Administration (FDA)

Diagnostic moléculaire par PCR

Les techniques discutées en amont ont donc toutes un certain nombre de défauts en pratique diagnostique, de ce fait les tests de biologie moléculaire et les techniques de PCR n'ont cessé de se développer jusqu'à devenir ce jour la méthode de diagnostic de référence en raison de leurs performances diagnostiques élevées. Les techniques de PCR ont une sensibilité très élevée [23–26], elles présentent cependant un certain nombre de défauts sur lesquels ont porté les récents développements : leur coût, la nécessité d'un personnel et de locaux spécialisés, un délai de rendu relativement long et la possibilité de détecter seulement un pathogène par test. Elles ont donc été régulièrement améliorées autour de ces différentes thématiques. Aujourd'hui les nouvelles techniques de PCR multiplex sont capables de détecter jusqu'à plusieurs dizaines de cibles en un seul test permettant la détection des virus influenza et de presque tous les autres virus respiratoires: influenza A et B, RSV A et B, parainfluenzae 1 à 4, adénovirus, rhinovirus, bocavirus, métapneumovirus, coronavirus (NL63, 2293, OC43) et un nombre variable de bactéries selon les kits (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Bordetella pertussis* et *parapertussis*).

Parmi tous ces tests PCR, certains permettent désormais d'obtenir les résultats en moins de deux heures dans un laboratoire : FilmArray® (BioFire, BioMérieux), ePlex® (GenMark). Ils ont aussi été déployés dans certains centres comme tests délocalisés, mais certaines manipulations restent encore un peu techniques et imposent d'être réalisées par un personnel qualifié. Toujours pour diminuer le temps-résultat, de nouvelles techniques de PCR sont en cours de développement et pensées plus spécifiquement pour le « point of care testing » (POCT), permettant aux médecins d'exécuter la technique au chevet du patient sans aucune manipulation de laboratoire et de donner une réponse rapide en moins de deux heures [27]. Un premier test multiplex développé ainsi est le test QIAstat-Dx respiratory panel (Qiagen), donnant une réponse en 70 min.

D'autres méthodes de PCR rapides non ou peu multiplexées existent. Parmi elles, les tests type ID NOW® sont des méthodes de diagnostic moléculaire plus simple (LAMP) et facile d'utilisation en « point of care ». Le principe repose sur une amplification isothermique à médiation par boucle permettant la détection des virus influenza A et B ou le VRS. Une étude multicentrique, menée en 2015, a montré que la sensibilité et la spécificité de l'Alere® étaient respectivement de 91,4% et 97,6% pour influenza A et 54,5% et 98,8% pour influenza B [28].

La deuxième génération ID NOW® atteint une sensibilité et une spécificité globales de 96,6% et 96,1% respectivement. La plupart des faux négatifs présentent une charge virale faible définie par un CT > 37 en RT-PCR (nombre de cycles de réplifications) [29].

Ainsi, même si ces tests ont une meilleure sensibilité que les TROD, leur réalisation nécessite quelques étapes de plus et leurs performances sont toujours inférieures au gold standard de la PCR [30].

	FilmArray® Respiratory Panel 2 plus (BioFire)	ePlex® Respiratory Pathogen Panel (GenMark Dx)	QiaStat® Respiratory Panel 2 (Qiagen)
Type de PCR	Point final	Point final	PCR temps réel (semi-quantitatif)
Durée de l'analyse	45 minutes	70 minutes	70 minutes
Marquage CE	Oui	Oui	Oui
Sensibilité	95.8%	93.3%	98%
Spécificité	99.7% [31]	97.4% [32]	99.9% [33]
Faisabilité aux urgences	Moyenne	Moyenne	Bonne
Virus détectés :			
Influenza (A & B)	x	x	x
VRS (A & B)	x	x	x
Rhinovirus/Entérovirus	x	x	x
Métapneumovirus	x	x	x
Coronavirus			
NL63	x	x	x
229E	x	x	x
OC43	x	x	x
HKU1	x	x	x
Parainfluenza (1 à 4)	x	x	x
Adénovirus	x	x	x
Bocavirus		x	x
MERS-Coronavirus	x	x	
SARS-CoV-2	x	x	x
Bactéries détectées :			
Mycoplasma pneumoniae	x	x	x
Chlamydia pneumoniae	x	x	x
Bordetella pertussis	x	x	x
Bordetella parapertussis	x		
Legionella pneumophila		x	x

Tableau 2. Liste des principales PCR multiplex adaptées pour l'utilisation en point of care

Utilité du diagnostic virologique rapide des infections respiratoires aux urgences

Plusieurs méthodes sont donc aujourd'hui disponibles à l'utilisation en POCT aux urgences, les TROD immunochromatographiques, les PCR isothermales (LAMP), les PCR simplex ou faiblement multiplexées (influenza-VRS) et enfin le panel diagnostic complet offert par la PCR multiplex (cf Tableau 2).

A ce jour, la grande majorité des études a été conduite avec les TROD du fait de leur facilité d'utilisation, de leur existence ancienne et de leur coût plus faible, malgré des performances diagnostiques moindres que les PCR. La réalisation d'un TROD ne nécessite pas une formation très longue et peut être effectuée par des infirmières aux urgences, sans impacter fortement le déroulement des soins [34]. Du fait des meilleures sensibilités de ces tests chez l'enfant, les pédiatres ont souvent recours aux TROD et de nombreuses études ont montré que leur utilisation évite des examens inutiles et guide la prescription d'antiviraux [35,36].

Concernant les PCR isothermales, type IDnow, une étude belge bi-centrique réalisée pendant trois mois et ayant inclus 253 malades (enfants et adultes) a montré que le recours à ce type de test a pu réduire le pourcentage d'hospitalisations dans environ 10 % des cas de patients positifs pour les virus influenza, de réduire la prescription d'antibiotiques de 46,4% ainsi que le nombre de prescriptions d'examen complémentaires de 42.9% [28]. Une étude anglaise multicentrique ayant inclus 589 malades sur 4 sites hospitaliers a démontré que le recours au diagnostic rapide IDnow pouvait entraîner une économie importante de l'ordre de £215 040 pour 1 000 malades, notamment en réduisant les placements en chambre seule non nécessaires chez les patients ayant des PCR négatives [37].

En ce qui concerne le recours à la PCR multiplex pour le diagnostic syndromique respiratoire aux urgences, les études sur les impacts bénéfiques sont très peu nombreuses malgré leur nécessité en regard du prix qui varie entre 80 et 150 euros.

L'essai contrôlé randomisé ResPOC [38] se déroulant en Angleterre entre janvier 2015 et avril 2016 a inclus 720 patients dont 362 dans le bras POCT utilisant la PCR multiplex FilmArray et 358 dans le bras de prise en charge classique avec des PCR ciblées ou multiplex faites au laboratoire à la demande du clinicien. Cet essai n'a pas démontré d'effet sur le critère de jugement principal qui était la durée d'antibiothérapie. En effet, la durée moyenne des antibiotiques ne différait pas entre les deux bras avec respectivement 7,2 jours et 7,7 jours dans le groupe PCR multiplex et le groupe témoin ($p=0,32$).

Néanmoins, la durée moyenne de séjour était plus courte dans le groupe POCT (5,7 jours) que dans le groupe témoin (6,8 jours) ($p = 0,0443$). Le traitement antiviral était aussi plus souvent

prescrit chez les patients ayant une PCR positive pour un virus influenza dans le groupe POCT 91% versus 65% dans le groupe témoin ($p = 0,0026$).

L'analyse Post Hoc de cette même étude a montré que chez les patients ayant une PCR positive dans le bras POCT, avec un délai de rendu de résultat $< 1,6h$ était associé à une durée de séjour moins importante (2,3 jours versus 5,1 jours soit une différence de 2,8 jours ; $p < 0,0001$) et à un arrêt précoce de l'antibiothérapie (OR 0,3 ,95% CI (0,1 to 0,9); $p=0,029$) [39].

Un autre essai anglais quasi randomisé réalisé entre janvier et juillet 2015 dans un service d'aval des urgences accueillant des patients avec des syndromes grippaux a aussi évalué l'impact de la PCR multiplex en POCT. Au total 545 patients ont été inclus, dont 334 dans le bras POCT et 211 dans le bras témoin. Cet essai n'a montré aucun impact de l'utilisation de la PCR multiplex en POCT sur la durée de séjour des patients ni sur la durée d'antibiothérapie [40].

Enfin un essai chinois contrôlé et randomisé conduit entre octobre 2017 et juillet 2018 a inclus 800 patients dont 398 dans le groupe POCT et 402 dans le groupe témoin. La durée du séjour à l'hôpital dans le groupe POCT était significativement plus courte (8,0 jours (IQR 7,0-11,0) versus 9.0 jours (IQR 7,0-12,0; $p < 0,001$) et le coût d'hospitalisation dans le groupe POCT était significativement plus bas (1 804,7 \$ (IQR 1 298,4 –2 633,8) contre 2 042,5 \$ (IQR 1 427,4–2 926,2); $p 0,002$) que le groupe témoin [41].

Particularité de la saison hivernale 2019-2020 liée à la pandémie de SARS-CoV-2

En décembre 2019, les premiers cas de pneumonies à SARS-CoV-2 ont été rapportés en Chine [42], et à ce moment-là, nul ne se doutait de l'ampleur qu'allait prendre la pandémie qui affecte le monde entier depuis plus d'un an. En mars 2021, la COVID-19 a déjà été responsable de plus de 117 millions d'infections et de plus de 2,6 million de décès dans le monde [43]. Cette pandémie a mis en difficulté les systèmes de soins dans les pays développés comme dans les pays en voie de développement. La plupart des pays ont eu recours à un ou plusieurs confinements pour réduire la progression de la pandémie avec des résultats variables en fonction du type et de la durée de ces confinements et de l'adhésion de la population [44,45].

Cliniquement, les patients infectés par le SARS-CoV-2 peuvent présenter les classiques symptômes du syndrome grippal ou ILI pour *Influenza Like Illness*. Les symptômes les plus fréquents sont alors la fièvre, les myalgies et la dyspnée. Ces symptômes ne permettent pas d'orienter vers les SARS-CoV-2 ou un pathogène particulier.[46]. Lors de l'émergence des premiers cas d'infection par le SARS-CoV-2 en Europe, les virus hivernaux saisonniers comme

les virus influenza, le rhinovirus ou le VRS circulaient encore pour complètement disparaître fin mars [47] D'autres patients infectés par le SARS-CoV-2 sont asymptomatiques. Les différentes estimations varient de 10 à 40% d'asymptomatiques parmi les patients infectés et une méta-analyse récente estime ce pourcentage à 17 % [48].

La RT-PCR en laboratoire est aussi le gold standard pour la détection du SARS-CoV-2, malgré un pourcentage de faux négatifs sur prélèvement nasopharyngé pouvant aller jusqu'à 29% [49]. Ces derniers faux négatifs concernent principalement des patients se présentant à une phase tardive de la maladie et pour lesquelles la réplication virale semble se localiser au niveau de l'arbre respiratoire bas. Mais la mauvaise compliance aux critères de qualité d'un prélèvement nasopharyngé peut aussi en être la cause. La proportion de ces patients a été estimée à 10% dans une méta-analyse menée sur la première vague de la pandémie [50]. La RT-PCR standard prend du temps, plus de 5h, et elle est réservée aux laboratoires spécialisés. Le délai de rendu de résultat peut donc s'élever à plus de 24 heures [51], ce qui peut entraîner des retards dans les diagnostics et l'instauration des précautions d'hygiène nécessaires, associés à un engorgement des services d'urgences.

Des techniques de PCR rapides et PCR multiplex au lit du patient ont vite été développées permettant de les utiliser largement dans la gestion initiale de la pandémie. En effet, plusieurs essais ont été publiés sur le recours à la RT-PCR SARS-CoV-2 en POCT comme cet essai britannique avec la CovidNudge plateforme qui évalue ses performances à une sensibilité de 94% (IC à 95% 86–98) avec une spécificité de 100% (99–100) par rapport à la RT-PCR faite au laboratoire [52].

Un autre essai britannique, prospectif et randomisé a été mené entre le 20 mars 2020 et le 29 avril 2020 à Southampton et a inclus 499 malades dans le groupe utilisant une mPCR SARS-CoV-2 délocalisée au urgences et 555 dans le groupe témoin, pour lequel les RT-PCR étaient réalisées au laboratoire.[53] Le délai médian d'obtention des résultats était de 1,7 h (IQR 1,6–1,9) dans le groupe POCT et de 21,3 h (IIQ 16,0–27,9) dans le groupe témoin (différence 19,6 h [19,0–20,3], $p < 0.0001$). La conclusion de cet essai est identique au précédent, la réduction du temps de rendu de résultat améliore la gestion du flux de patient et l'instauration des mesures d'hygiène adaptées (Cf. Tableau 3).

	Point-of-care testing*	Control*	Between-group difference (95% CI)†	p value
Time to results, h	1.7 (1.6 to 1.9)	21.3 (16.0 to 27.9)	-19.6 (-19.0 to -20.3)	<0.0001
COVID-19 positive	197/499 (39%)	155/555 (28%)	11.5% (5.8 to 17.2)	0.0001
Admitted for >24 h	428/499 (86%)	421/555 (76%)	10.0% (5.0 to 14.7)	<0.0001
Transferred from assessment area to correct definitive clinical area on the basis of test result‡	313/428 (73%)	242/421 (57%)	15.7% (9.1 to 22.0)	<0.0001
Time from admission to arrival in a definitive clinical area‡, h	8.0 (6.0 to 15.0)	28.8 (23.5 to 38.9)	-20.8 (-18.4 to -21.2)	<0.0001
Bed moves between admission and arrival in definitive clinical area‡	<0.0001
0	43/313 (14%)	0/236
1	244/313 (78%)	163/236 (67%)
2	26/313 (8%)	56/236 (23%)
3	0/313	12/236 (5%)
4	0/313	4/236 (2%)
5	0/313	1/236 (<1%)
Mean (SD)	0.9 (0.5)	1.4 (0.7)	-0.5 (-0.4 to -0.6)	<0.0001
COVID-19-positive patients enrolled into other COVID-19 trials	124/197 (63%)	104/155 (67%)	-4.2% (-14.0 to 5.9)	0.42
Time from admission to enrolment into other COVID-19 trials, days	1.0 (1.0 to 3.0)	3.0 (2.0 to 4.5)	-2.0 (-1.0 to -2.0)	<0.0001
Antibiotics used	418/496 (84%)	387/555 (70%)	14.6% (9.5 to 19.5)	<0.0001
Length of stay, days	5.1 (2.0 to 9.2)	4.2 (1.2 to 9.6)	0.9 (0 to 1.0)	0.017
Intensive care unit admission	64/499 (13%)	42/555 (8%)	5.2% (0.2 to 8.9)	0.0039
In-hospital mortality	67/494 (14%)	69/555 (12%)	1.1% (-2.9 to 5.2)	0.58
30-day mortality	80/440 (18%)	86/555 (15%)	2.6% (-2.0 to 7.3)	0.26

*Data are n/N (%) or median (IQR), unless otherwise specified. †Point-of-care testing group minus control group.
‡Assessed in patients admitted for >24 h; definitive clinical area refers to a designated COVID-19-positive or COVID-19-negative ward.

Tableau 3 Mesure de l'impact du recours à la PCR SARS-COV-2-CoV2 en POCT[54].

Un autre essai a utilisé une PCR isothermale dont les performances diagnostiques semblaient correctes avec un indice de corrélation de Cohen de 0.96 avec la RT-PCR au laboratoire [55]. En comparant près de 1 000 tests avant et après la mise en place de la technique délocalisée, le délai médian de rendu de résultat était abaissé de 26,4h à 2,6h, le temps médian jusqu'au placement définitif en chambre à partir de l'admission est abaissé de 23,4h (8,6-41,9) contre 17,1 h (9,0-28,8) (p = 0,02) et la durée moyenne de séjour dans les services « d'attente » du COVID-19 est abaissée de 58,5 h à 29,9 h (p <0,001).

Toutes ces études convergent vers l'intérêt d'un délai de rendu de résultat virologique rapide afin de fluidifier les services d'accueil des urgences, d'améliorer les mesures de précautions permettant ainsi réduire les épidémies nosocomiales et même dans certains cas de réduire le nombre d'examens complémentaires.

Problématique et objectif de la thèse

Ce travail de thèse a débuté en 2018, soit au moment des premières grandes études sur l'impact des techniques de diagnostic syndromique respiratoire utilisées de façon délocalisée dans les services d'urgences.

Plusieurs tests POCT non infectieux sont largement utilisés aux urgences, notamment les gaz du sang, les bandelettes urinaires ou bien encore les appareils de mesure de la glycémie, mais les tests de biologie moléculaire qui nécessitent encore plus de rigueur lors des manipulations afin d'éviter les risques de contaminations et de faux positifs ne sont pas encore répandus dans ces services.

Plusieurs études ont cependant été menées pour évaluer si les nouvelles méthodes de mPCR étaient adaptées, efficaces et utiles en approche de biologie délocalisée aux urgences. Elles ont montré des résultats contradictoires sur l'impact du diagnostic syndromique des infections respiratoires par mPCR aux urgences. Certaines ont retrouvé un impact sur la durée de séjour ou la prescription d'antibiotiques et d'antiviraux mais d'autres n'ont pas retrouvé ces effets à l'exception d'une meilleure prescription des antiviraux. Aucune ne donnait d'estimation claire de l'impact sur le placement en chambre seule. Or une étude évaluant la relation entre l'admission en chambre double et la grippe nosocomiale a montré un risque plus élevé de contracter la grippe chez les patients admis en chambre double par rapport à ceux placés en chambre simple [56]. Dans une autre étude, la même équipe a estimé que le risque de grippe nosocomiale était largement augmenté lorsque le voisin de chambre présentait un syndrome grippal [57]. L'isolement des patients avec des virus pathogènes comme les virus influenza en chambre seule est donc la pierre angulaire des précautions pour lutter contre les épidémies nosocomiales avec bien sûr le respect des précautions gouttelettes, le port de masques et l'hygiène des mains [58].

Dans le travail développé au cours de cette thèse, nous avons :

- Réalisé une revue narrative des tests de diagnostic rapides de maladies infectieuses qui pourraient éventuellement être utilisés aux urgences et de leurs performances (Bouzid D et al, Clin Microb Infect 2020) [59].
- Étudié l'impact du délai de rendu de la PCR réalisée au laboratoire de virologie sur la décision de placement en chambre seule des patients admis au SAU pour un syndrome grippal (Bouzid D et al, Plos One 2020)[60].

- Étudié la faisabilité de l'implantation d'un test syndromique respiratoire par mPCR multiplex aux urgences de l'hôpital Bichat Claude Bernard, puis évalué l'impact de ces tests délocalisés sur la prise en charge de nos patients consultants pour une suspicion de pneumonie (Bouzig D et al, JHI 2020)[61].
- Étudié l'impact de la PCR multiplex réalisées aux urgences versus au laboratoire de virologie sur la prise en charge des patients consultants pour une suspicion de pneumonie avec un essai clinique contrôlé (Travail en revue mineure chez JAC).
- Lors de la pandémie de SARS-CoV-2, nous avons aussi étudié les différences de présentation clinico-biologique entre les patients infectés par le SARS-CoV-2 ou un autre virus respiratoire, ainsi que la fréquence et le pronostic associés aux coinfections du SARS-CoV-2 avec un autre virus respiratoire (Bouzig D et al, Plos one 2020, Bouzig et al. Influenza and other respiratory viruses 2021) [47,62].

Tests de diagnostic rapide pour les maladies infectieuses aux urgences.

Contexte et objectif

Les tests de diagnostic microbiologique rapide (tests rapides) sont mis en œuvre dans de nombreux laboratoires dans le but d'accélérer les démarches diagnostiques. Depuis déjà une dizaine d'années, certaines sont bien installées dans les services d'accueil des urgences, comme les bandelettes urinaires ou les appareils à glycémie, tandis que d'autres se démocratisent de plus en plus, notamment dans le domaine des maladies infectieuses. Pour ce dernier cas, elles ont un rôle primordial à jouer pour prévenir les épidémies nosocomiales et permettre d'assurer la prise en charge appropriée le plus vite possible.

Un diagnostic rapide des pathologies infectieuses conduirait donc à une prise en charge plus rapide et doit pouvoir améliorer le pronostic du malade, la sécurité des soins et la gestion des flux.

Si plusieurs types de tests rapides pour différents tableaux cliniques sont actuellement disponibles, leur utilisation réussie dans un service d'accueil des urgences nécessite une évaluation préalable minutieuse des performances, des avantages potentiels pour les soins et bien évidemment la considération des coûts et surcoûts [63].

Le but de cette revue narrative était de donner un aperçu des grandes familles de tests rapides actuellement disponibles pour les maladies infectieuses aux urgences, d'apporter une description détaillée de leurs performances actuelles et de discuter de leur impact potentiels ou établi sur les pratiques de soins.

Méthodes

Une recherche a été menée sur Pubmed, au cours du mois d'août 2019 pour identifier les études sur les TDR pour les maladies infectieuses utilisés dans un service d'accueil des urgences en utilisant les termes certains mots-clés MeSH suivant :

“RIDT”, “point of care”, “panel”, “ED”, “emergency Department”, “respiratory tract infection”, “URTI”, “LRTI”, “influenza”.

Les critères d'inclusion étaient (i) des tests commerciaux approuvés par la Food and Drug Administration (FDA) ou ayant la conformité européenne avec le marquage de diagnostic in vitro (CE-IVD) et avec des données publiées sur des échantillons cliniques ; (ii) la capacité à fonctionner sur des systèmes entièrement automatisés; (iii) et un temps de rendu des résultats inférieur ou égal à 2 heures.

Résultats

Compte tenu du sujet de la thèse, nous développerons uniquement les résultats en rapport avec les tests rapides pour les infections respiratoires basses.

Tests rapides réalisés sur des échantillons d'urine

Les tests antigéniques urinaires rapides sont largement utilisés pour le diagnostic des infections respiratoires à *S. pneumoniae* et *L. pneumophila*. Ces tests rapides d'antigénuries pour la détection de *S. pneumoniae* présentent des sensibilités allant de 62% à 66% par rapport aux hémocultures et ECBC [64]. Les performances des tests de détection de l'antigène urinaire *L. pneumophila* varient selon plusieurs facteurs [65,66], y compris (i) le type de test, avec une performance meilleure pour les tests d'immunofluorescence; (ii) type d'échantillon (iii) le traitement préalable des échantillons; et (iv) sérotype, avec des sensibilités plus élevées pour *L. pneumophila* sérotype 1. Les faux positifs peuvent être dus à une infection récente à *L. pneumophila* ou *S. pneumoniae* ou à la vaccination anti-pneumococcique, respectivement, justifiant une interprétation prudente, en l'absence de cultures concomitantes.

Selon les recommandations actuelles, un traitement antibiotique doit être instauré immédiatement après le diagnostic de pneumonie communautaire, ce traitement comprend une thérapie empirique dirigée contre le *S. pneumoniae*. La confirmation microbiologique rapide offre en théorie la possibilité de faire une désescalade des antibiotiques. Cependant, dans la pratique, la faible sensibilité et spécificité des tests antigéniques urinaires pour *S. pneumoniae* [48,59] ne permettent pas une telle désescalade et une grande proportion de patients restent traités avec des antibiotiques à plus large spectre malgré ce test à l'intérêt du coup très limité [67–69].

Tests rapides réalisés sur des échantillons respiratoires

Parmi les panels développés pour la détection large des virus respiratoires à partir d'échantillons nasopharyngés, plusieurs sont désormais disponibles sur un système automatisé avec des délais d'exécution d'environ une heure. Ils permettent la détection des agents pathogènes responsables des infections des voies respiratoires les plus courantes : virus et certaines bactéries atypiques, dont principalement *Bordetella pertussis*, *Chlamydia pneumoniae* et *Mycoplasma pneumoniae*. Les performances diagnostiques, comparées aux tests PCR de référence, sont

bonnes (sensibilité et spécificité de 80% à 100% pour toutes les cibles). À noter que, pour certains panels, les cibles bactériennes, plus rares que les cibles virales, ont été validées avec moins de dix échantillons et les caractéristiques de performance de la PCR bactérienne ont parfois été signalées comme étant inférieures à celles de la PCR virale ou des PCR spécifiques bactériennes [31].

Pour le diagnostic des infections des voies respiratoires inférieures aux urgences, un délai d'exécution court est un paramètre clé pour un traitement rapide et adapté, comme pour mettre en œuvre les mesures de précautions nécessaires comme pour les virus influenza [60,70].

Discussion

Une intégration appropriée des tests rapides dans l'environnement particulier d'un service d'accueil des urgences est l'élément le plus important à ne pas négliger. Si l'objectif principal est l'instauration rapide des mesures de précautions gouttelettes (par exemple pour la détection des virus influenza en période d'épidémie), ou l'administration adaptée des traitements anti-infectieux ou encore pour la gestion du flux des patients. Dans ce dernier cas, nous pouvons imaginer que certains de ces tests rapides soient réalisés d'emblée par l'infirmière responsable du tri des patient ou infirmière d'accueil et d'orientation (IAO).

Cette revue narrative donne une liste conséquente, même si non exhaustive, de tests rapides utilisables dans des services d'accueil des urgences. Ces méthodes, malgré des performances diagnostiques très bonnes, doivent s'intégrer intelligemment dans un service d'accueil des urgences qui a ses propres contraintes afin de pouvoir avoir un impact positif sur la prise en charge du patient. La confirmation diagnostique au laboratoire conventionnelle reste très souvent nécessaire et ces tests ont très souvent des coûts plus élevés que les tests au laboratoire. Des études pragmatiques avec une analyses coût efficacité sont donc nécessaires à réaliser afin de conclure de façon plus formelle sur la place des tests rapides et leur balance coût-efficacité dans un service d'accueil des urgences.

Un test microbiologique rapide doit avoir à la fois de bonnes performances diagnostiques et un délai de rendu court pour pouvoir s'intégrer dans l'organisation d'un SAU et impacter au maximum la prise en charge des patients.

Pour vérifier l'intérêt éventuel d'un test délocalisé aux urgences de l'hôpital Bichat, nous avons dressé un état des lieux des délais de rendu de résultat du laboratoire centralisé de virologie et de l'impact de ces délais sur les placements en chambre seule.



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Narrative review

Rapid diagnostic tests for infectious diseases in the emergency department

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ABSTRACT

Background: Rapid diagnostic tests (RDTs) for infectious diseases, with a turnaround time of less than 2 hours, are promising tools that could improve patient care, antimicrobial stewardship and infection prevention in the emergency department (ED) setting. Numerous RDTs have been developed, although not necessarily for the ED environment. Their successful implementation in the ED relies on their performance and impact on patient management.

Objectives: The aim of this narrative review was to provide an overview of currently available RDTs for infectious diseases in the ED.

Sources: PubMed was searched through August 2019 for available studies on RDTs for infectious diseases. Inclusion criteria included: commercial tests approved by the US Food and Drug Administration (FDA) or Conformité Européenne (CE) *in vitro* diagnostic devices with data on clinical samples, ability to run on fully automated systems and result delivery within 2 hours.

Content: A nonexhaustive list of representative commercially available FDA- or CE-approved assays was categorized by clinical syndrome: pharyngitis and upper respiratory tract infection, lower respiratory tract infection, gastrointestinal infection, meningitis and encephalitis, fever in returning travellers and sexually transmitted infection, including HIV. The performance of tests was described on the basis of clinical validation studies. Further, their impact on clinical outcomes and anti-infective use was discussed with a focus on ED-based studies.

Implications: Clinicians should be familiar with the distinctive features of each RDT and individual performance characteristics for each target. Their integration into ED work flow should be preplanned considering local constraints of given settings. Additional clinical studies are needed to further evaluate their clinical effectiveness and cost-effectiveness. **D. Bouzid, Clin Microbiol Infect 2021;27:182**

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Introduction

Rapid diagnostic tests (RDTs) for infectious diseases have been implemented in many laboratories and emergency departments (EDs), with the goal of expediting the diagnosis of infectious

diseases, infection prevention, appropriate initial management and facilitation of antimicrobial stewardship in the ED, where rapid clinical decisions must be undertaken in the context of overcrowding and time pressure [1]. Even though multiple RDTs are currently available, their successful implementation in the ED requires careful assessment of performance characteristics, potential benefits to patient care and cost considerations, as well as a well-organized implementation plan to optimize their impact [2].

The goal of this narrative review was to provide an overview of currently available RDTs for infectious diseases in the ED with a detailed description of their performance; and to discuss their impact on patient care.

Methods

A comprehensive PubMed search was conducted through August 2019 to identify studies on RDTs for infectious diseases in ED department using the following MeSH terms and keywords: RDT, point of care, panel, turnaround time <2 hrs, ED, emergency service, pharyngitis, respiratory tract infection, URTI, LRTI, influenza, RSV, urinary antigen, pneumococcal urinary antigen, *Legionella* urinary antigen, gastrointestinal infection, central nervous system infection, meningitis, encephalitis, fever returning traveller, sexually transmitted infection, STI.

Inclusion criteria were commercial tests approved by the US Food and Drug Administration (FDA) or Conformité Européenne (CE) *in vitro* diagnostic with data published on clinical samples; ability to run on fully automated systems; and result delivery within 2 hours [3].

Assay performance characteristics, including sensitivity and specificity, were outlined on the basis of published clinical validation studies whenever available. In the absence of test comparison against a reference standard assay, the reported positive and negative percentage agreement in identified clinical studies or manufacturer performance data were not reported to avoid any misinterpretation.

Overview of available tests

A nonexhaustive list of representative commercially available FDA- or CE-approved RDTs is provided in Table 1 [4–39]. Of note, all assays discussed in this review are qualitative assays. When available, we describe the evidence for the impact of tests on clinical outcomes and anti-infective use in the ED (Table 2) [6,32,40–55].

Pharyngitis and upper respiratory tract infections

Upper respiratory tract infection is the leading infectious cause of visits in the ED. In patients with pharyngitis, clinical scoring systems and rapid tests are recommended to target antibiotic use.

For group A *Streptococcus* pharyngitis, diagnosis and immunofluorescence-based assay demonstrated higher diagnostic performances compared to an immunochromatographic rapid antigen detection test in paediatric patients presenting with pharyngitis with a McIsaac score of ≥ 2 ; the negative predictive value of the immunofluorescence-based assay was also higher (92%) in this paediatric population, with a group A *Streptococcus* prevalence of 37% [4].

In patients with a high likelihood of streptococcal infection, guidelines recommend the use of RDTs because they are associated with decreased antibiotic use in paediatric ED populations [56]. However, the usefulness of clinical scores in children appears to be lower than for adults as a result of the different clinical presentation of sore throat in infants and young children. Point-of-care PCR assays demonstrated improved performance compared to culture

or rapid antigen detection test as well as reduced unnecessary antibiotic use in paediatric studies [5–7].

In patients with influenza-like illness, implementation of the FilmArray multiplex PCR respiratory panel in the ED was associated with shorter times to diagnosis for all respiratory viruses, shorter duration of antibiotic use, decreased hospitalization rates, shortened length of stay (LOS) and reduced costs [41,45]. A meta-analysis evaluated the clinical impact of molecular RDTs for respiratory viruses by analysing 56 individual test accuracy studies, and it showed that compared to conventional molecular assays, RDTs did not reduce antibiotic use and duration, isolation measures or admission rates but increased receipt of oseltamivir in positive cases of influenza cases and reduced LOS [57].

Lower respiratory tract infections

The most frequent lower respiratory tract infections seen in the ED include acute bronchitis, community-acquired pneumonia, influenza-like illness and acute chronic obstructive pulmonary disease exacerbation. Current guidelines recommend that urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 antigens should be performed for community-acquired pneumonia patients with severe illness, and for legionellosis when clinically or epidemiologically suspected. Rapid multiplex PCR tests from nasopharyngeal swabs for atypical bacteria and respiratory viruses should also be considered.

RDTs performed on urine specimens

Rapid urine antigen tests are widely used for the diagnosis of *S. pneumoniae* and *L. pneumophila* respiratory infections. Rapid tests for *S. pneumoniae* detection present sensitivities ranging from 62% to 66% compared to blood or sputum culture [8]. The performance of *L. pneumophila* urinary antigen detection tests varies according to several factors [9,58], including (a) assay type, with improved performance for immunofluorescence tests; (b) sample type (clinical vs. simulated urine samples prepared with strains of *L. pneumophila* serogroup 1 are best detected); (c) preanalytic sample processing; and (d) serogroup, with higher sensitivities for *L. pneumophila* serogroup 1. False-positive results can be due to recent *L. pneumophila* or *S. pneumoniae* past infection or pneumococcal vaccination, respectively, warranting cautious interpretation in the absence of concomitant cultures.

According to guidelines, antibiotic treatment should be initiated immediately after community-acquired pneumonia diagnosis. Such treatment includes empiric therapy of *S. pneumoniae*. Rapid microbiologic confirmation theoretically offers the opportunity for antibiotic de-escalation. However, in practice, the poor sensitivity and specificity of urinary antigen testing for *S. pneumoniae* [48,59] do not allow such de-escalation, and a large proportion of patients remain treated with broader-spectrum antibiotics [49,60,61].

RDTs performed on respiratory specimens

Among panels developed for broad respiratory virus detection from nasopharyngeal samples, several are now available on a fully automated system with turnaround times of about an hour (Table 1). They allow the detection of all the most common respiratory viruses and some atypical bacteria, including *Bordetella pertussis*, *Bordetella parapertussis*, *Chlamydomphila pneumoniae* and *Mycoplasma pneumoniae*. Analytical performance characteristics, compared to reference PCR assays, are good to excellent (sensitivity and specificity from 80% to 100% for all targets). Of note, some bacterial targets have been validated with fewer than ten positive samples, and performance characteristics of bacterial PCR have

Table 1
Nonexhaustive list of commercially available US Food and Drug Administration– and Conformité Européenne–approved point-of-care tests in infectious diseases classified by syndrome or disease of interest

Syndrome or disease	Specific test, duplex or panel	Targeted pathogens	Technique	Clinical specimen types	Trade names of some available assays	Test performance characteristics ^a			Reference
						Sensitivity	Specificity	TAT (minutes)	
Upper respiratory tract infections	Specific	Group A <i>Streptococcus</i>	LFA	Pharyngeal swabs	Sofia StrepA FIA	84.9%	96.8%	5	[4]
	Specific	Group A <i>Streptococcus</i>	LFA	Pharyngeal swabs	TestPack Strep A	75.3%	98.1%	5	[4]
	Specific	Group A <i>Streptococcus</i>	rPCR	Pharyngeal swabs	AmpliVue GAS Assay	98.3%	93.2%	60	[5]
	Specific	Group A <i>Streptococcus</i>	rPCR	Pharyngeal swabs	cobas Liat Strep A Assay	95.5%	99.3%	15	[6]
	Specific	Group A <i>Streptococcus</i>	rPCR	Pharyngeal swabs	Xpert Xpress Strep A	100%	79.3%	25	[7]
Lower respiratory tract infections	Specific	<i>Streptococcus pneumoniae</i>	LFA	Urine samples	Sofia <i>S. pneumoniae</i> FIA	66%	100%	10	[8]
	Specific	<i>S. pneumoniae</i>	LFA	Urine samples	BinaxNow <i>Streptococcus pneumoniae</i> Antigen Card	62%	98%	15	[8]
	Specific	<i>Legionella pneumophila</i>	LFA	Urine samples	BinaxNOW <i>Legionella</i> Urinary Antigen Card	79.7%	97.1%	15	[9]
	Specific	<i>Mycoplasma pneumoniae</i>	LAMP	Throat swabs	illumigene <i>Mycoplasma</i> Direct DNA amplification assay	87%	97.9%	60	[10]
	Specific	Influenza A and B	rRT-PCR	NP swabs	cobas Influenza A/B assay	IA: 97.5% IB: 96.9%	IA: 97.9% IB: 97.9%	20	[11]
	Specific	Influenza A and B	rRT-PCR	NP swabs	ID NOW INFLUENZA A & B (formerly Alere i. Influenza A & B)	NA	NA	15	[12]
	Specific	Influenza A and B	LFA	Nasal swabs, NP swabs, NP aspirate/wash	Sofia influenza A + B FIA	IA: 82.2% IB: 77.8%	IA: 100% IB: 100%	15	[13]
	Specific	RSV	rRT-PCR	NP swabs/aspirate	ID NOW RSV (formerly Alere I RSV)	100%	97%	15	[14]
	Panel	Influenza A/B, RSV	rRT-PCR	NP swabs	cobas Influenza A/B & RSV	NA	NA	20	[15]
	Panel	Influenza A/B, RSV	rRT-PCR	Nasal wash fluid samples/aspirates and NP swabs	Xpert Flu/RSV XC	NA	NA	40	[16]
	Panel	Human adenovirus, human metapneumovirus, rhinovirus/enterovirus, influenza A/B, parainfluenza, RSV, <i>Bordetella pertussis</i> , <i>Chlamydia pneumoniae</i> , <i>Mycoplasma pneumoniae</i>	r(RT-)PCR	NP swabs	BioFire FilmArray Respiratory Panel	NA	NA	65	[17,18]
	Panel	Human adenovirus, coronavirus, human metapneumovirus, rhinovirus/enterovirus, influenza A/B, parainfluenza, RSV, MERS-Cov, <i>Bordetella pertussis</i> , <i>Chlamydia pneumoniae</i> , <i>Mycoplasma pneumoniae</i> , <i>Bordetella parapertussis</i>	r(RT-)PCR	NP swabs	BioFire FilmArray Respiratory Pane12 plus (RP2plus)	NA <i>M. pneumoniae</i> : 95.8%	NA <i>M. pneumoniae</i> : 99.7%	45	[19]
	Panel	Human adenovirus, coronavirus, human metapneumovirus, human rhinovirus/enterovirus, influenza A/B, parainfluenza, RSV-A1-B, <i>Chlamydia pneumoniae</i> , <i>Mycoplasma pneumoniae</i>	r(RT-)PCR	NP swabs	eFlex Respiratory Pathogen (RP) Panel	NA	NA	90	[20]
Gastro-intestinal infections	Specific	<i>Clostridium difficile</i>	rPCR	Stool samples	Xpert <i>C. difficile</i> BT	21.5%	100%	47	[21,22]
	Specific	<i>C. difficile</i>	rPCR	Stool samples	cobas Cdiff test	92.9%	98.7%	20	[23]
	Specific	<i>C. difficile</i>	EIA	Stool samples	Xpert <i>C. difficile</i> Toxin A/B Test	48%	84%	20	[24]

	Specific	<i>C. difficile</i>	EIA	Stool samples	VIDAS <i>C. difficile</i> GDH and VIDAS <i>C. difficile</i> Toxin A & B	80–89.8%	96.7–97.3%	50	[25]
	Panel	<i>Campylobacter (jejuni, coli and upsaliensis)</i> , <i>Clostridium difficile</i> (toxin A/B), <i>Plesiomonas shigelloides</i> , <i>Salmonella</i> , <i>Yersinia enterocolitica</i> , <i>Vibrio (parahaemolyticus, vulnificus, cholerae)</i> , <i>Escherichia coli</i> O157, enteroaggregative <i>E. coli</i> (EAEC), enteropathogenic <i>E. coli</i> (EPEC), enterotoxigenic <i>E. coli</i> (ETEC) It/st, Shiga-like toxin-producing <i>E. coli</i> (STEC) stx1/stx2 <i>E. coli</i> O157, <i>Shigella/enteroinvasive E. coli</i> (EIEC), adenovirus F 40/41, astrovirus, norovirus GI/GII, rotavirus A, sapovirus (I,II, IV, and V), <i>Cryptosporidium</i> , <i>Cyclospora cayentanensis</i> , <i>Entamoeba histolytica</i> , <i>Giardia lamblia</i>	rPCR	Stool samples	BioFire FilmArray GI Panel	100% for 12/22 targets ≥94.5% for an additional 7/22 targets	≥97.1% for all panel targets	60	[26]
Central nervous system infections	Duplex	<i>Cryptococcus neoformans</i> , <i>Cryptococcus gattii</i>	LFIA	Serum, CSF samples	CrAg LFA	100%	99.8%	20	[27]
	Specific	<i>S. pneumoniae</i>	LFIA	CSF samples	BinaxNow <i>Streptococcus pneumoniae</i> Antigen Card	95.4–100%	100%	15	[28]
	Specific	<i>Enterovirus</i>	rRT-PCR	CSF samples	NudiSENS EasyQ Enterovirus v1.1	NA	NA	120	[29]
	Panel	<i>E. coli</i> K1, <i>Haemophilus influenzae</i> , <i>Listeria monocytogenes</i> , <i>Neisseria meningitidis</i> , <i>S. pneumoniae</i> , <i>Streptococcus agalactiae</i> , enterovirus, HSV-1/2, VZV, CMV, HHV-6, human parechovirus, <i>C. neoformans</i> / <i>C. gattii</i>	r(RT)-PCR	CSF samples	BioFire FilmArray Meningitis/Encephalitis (ME) Panel	<i>E. coli</i> K1: 100% <i>Haemophilus influenzae</i> : 100% (n = 1) <i>L. monocytogenes</i> : NA <i>N. meningitidis</i> : NA <i>S. agalactiae</i> : 0% (n = 1) <i>S. pneumoniae</i> : 100%	<i>E. coli</i> K1: 99.9% <i>H. influenzae</i> : 99.9% <i>L. monocytogenes</i> : 100% <i>N. meningitidis</i> : 100% <i>S. agalactiae</i> : 99.9% <i>S. pneumoniae</i> : 99.2%	65	[30]
Fever in the returning traveller	Specific	<i>Plasmodium</i> spp.	LFIA	Whole blood samples	BinaxNOW Malaria	All patients 84.2% Patients without antimalarial therapy: 92.9%	99.8%	15	[31]
	Specific	<i>Plasmodium</i> spp.	LAMP	Whole blood samples	Illumigene Malaria DNA amplification assay	98.1%	97.6%	10	[32]
	Specific	Dengue virus	EIA	Plasma, serum samples	NS1 Ag detection ⁵				[33]
					<ul style="list-style-type: none"> • Dengue NS2 Ag Strip 52% • OnSite Dengue Ag Rapid Test 40% • Dengue Early Rapid Test 60% • SD Bioline Dengue Duo 59% IgM detection <ul style="list-style-type: none"> • Dengue IgG/IgM Rapid Test Device 63% • OnSite Dengue IgG/IgM Combo 46% • SD Bioline Dengue Duo 89% 	<ul style="list-style-type: none"> 77% 76% 75% 78% <ul style="list-style-type: none"> 91% 86% 80% 	<ul style="list-style-type: none"> 30 30 20 20 <ul style="list-style-type: none"> 20 30 20 		

(continued on next page)

Table 1 (continued)

Syndrome or disease	Specific test, duplex or panel	Targeted pathogens	Technique	Clinical specimen types	Trade names of some available assays	Test performance characteristics ^a			Reference
						Sensitivity	Specificity	TAT (minutes)	
Sexually transmitted infections	Duplex	<i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i>	rPCR	Vaginal/endocervical and urine samples	Xpert CT/NG	<i>C. trachomatis</i> in female endocervical, vaginal, urine samples: 97.4%, 98.7%, 97.6% <i>C. trachomatis</i> in male urine samples: 97.5% <i>N. gonorrhoeae</i> in female subjects in endocervical, vaginal, urine samples: 100%, 100%, 95.6% <i>N. gonorrhoeae</i> in male urine samples: 98%	<i>C. trachomatis</i> in female and male samples: ≥99.4% <i>N. gonorrhoeae</i> in female and male samples: ≥99.8%	90	[34]
	Duplex	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i>	rPCR	Endocervical and ureteral samples	Gen-Probe PACE2C system for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoea</i> DETERMINE SYPHILIS TP	96.3%	98.8%	95	[35]
	Specific	<i>Treponema pallidum</i>	LFIA	Serum, plasma, whole blood samples	DETERMINE SYPHILIS TP	95.6–98.4%	97.3–95.7%	15	[36]
	Specific	<i>T. pallidum</i>	LFIA	Serum, plasma, whole blood samples	VisiTest Syphilis	57%	99%	30	[37]
	Specific	<i>T. pallidum</i>	LFIA	Serum, plasma, whole blood samples	Syphicheck-WB	67.4%	98.4%	15	[38]
	Specific	HIV		Blood samples	Antibody detection • EXACTO TEST HIV Self-test • INSTI HIV • Stat-View HIV-1/2 • Vika HIV-1/2 Antibody/antigen detection • Determine HIV-1/2 Ag/Ab Combo	(sensitivity for HIV-1 M Ab) 100% 100% 100% 100% 99.5% 100%	98.5% 100% 100% 100% 99.5% Antigen p24: 99.5% Antibodies: 100%	20 30 Immediately 20 30 40	[39]

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EIA, enzyme immunoassay; FIA, fluorescent immunoassay; HSV, herpes simplex virus; LAMP, loop-mediated isothermal amplification; LFIA, lateral flow immunoassay; NA, not applicable; NP, nasopharyngeal; r(RT-)PCR, real-time (reverse transcription-)polymerase chain reaction; RSV, respiratory syncytial virus; SSTI, skin and soft tissue infection; TAT, turnaround time; VZV, varicella zoster virus.

^a The performance characteristics of the assays are described as sensitivity and specificity according to published clinical validation studies when available. In the absence of test comparison against a reference standard assay, the reported positive and negative percentage agreement in the clinical studies reviewed were not reported to avoid misinterpretation.

^b Sensitivity has been extracted from the 'acute infection' population and specificity has been extracted from the 'naive individuals' population described in the corresponding reference.

Table 2
Clinical studies evaluating clinical impact of RDT use in ED

Syndrome or disease	Approach and targeted pathogens	Test brand	Population (n)	Study design	Findings	Reference
Upper Respiratory tract infections	Group A <i>Streptococcus</i> RADT	QuickVue (Quidel)	Infants (223)	SSPS	After using RADT, antibiotic prescriptions decreased by 42.6%. Compared with RADT, POC PCR resulted in significantly greater appropriate antibiotic use (97.1% vs. 87.5%; $p = 0.0065$)	[40]
	Group A <i>Streptococcus</i> PCR	cobas Liat Strep A (Roche)	Infants (275)	SSPS		[6]
Lower Respiratory tract infections	mPCR in ED vs. usual tests in central laboratory	FilmArray (BioFire, bioMérieux)	Infants (1136)	Single-centre retrospective	mPCR in ED decreases the duration of antibiotic use (from 3.2 to 2.8 days $p = 0.003$), the length of inpatient stay (from 3.4 to 3.2 days $p = 0.03$).	[41]
	mPCR in ED vs. usual tests in central laboratory	FilmArray (BioFire, bioMérieux)	Adults (720)	SSPS	mPCR in ED decreases the duration of antibiotic use (from 6.5 to 2.9 days, $p = 0.0009$), the hospital length of stay (from 6.8 to 5.7 days, $p = 0.004$)	[42]
	mPCR in ED vs. usual tests in central laboratory	FilmArray (BioFire, bioMérieux)	Adults (606)	SSPS	No association between respiratory PCR POC testing and length of stay but a reduction in the median time to the first dose of antiviral (from 60.4 to 24h) and appropriate treatment of mycoplasma infection	[43]
	Influenza PCR	cobas Liat (Roche)	Adults (620)	Multicentre retrospective	Antivirals were prescribed more often in patients that tested positive by Liat PCR (82.4%) than in those testing positive by either RIDT or reflex PCR (69.9%; $P < 0.05$)	[44]
	Influenza PCR	FilmArray (BioFire, bioMérieux)	Adults (337)	Single-centre retrospective	Diagnosis of influenza by FilmArray was associated with significantly lower ORs for admission ($p = 0.046$), length of stay ($p = 0.040$), duration of antimicrobial use ($p = 0.032$), and number of chest radiographs ($p = 0.005$).	[45]
	Influenza RADT	QuickVue (InGen)	Infants (170)	SSPS	Positive RADT enabled a significant decrease in orders for chest x-rays (64.4% vs. 45.8%, $p < 0.05$) and laboratory tests (71.1% vs. 41.1%, $p < 0.05$).	[46]
	Influenza immunoassay	Binax NOW (Alere)	Adults + infants (827)	Multicentre prospective	For a cohort of 1000 participants, annual estimated nondiagnostic cost savings with Alere are €215040.	[47]
	Pneumococcus (SP) and legionella (LP) urinary antigen	Binax NOW (Alere)	Adults (1941)	Epic study multicentre prospective	IDSA/ATS indications had 61% sensitivity (95% CI 49–71) and 39% specificity (95% CI 37–41) for SP, and 63% sensitivity (95% CI 44–79) and 35% specificity (95% CI 33–37) for LP.	[48]
Pneumococcus (SP) and legionella (LP) urinary antigen	Binax NOW (Alere)	Adults (1224)	Single-centre retrospective	Only 7 tests led to appropriate antimicrobial modification, and since 972 tests had no impact, we estimate that potential cost savings, if the test had not been used, would have been 26,244 € during a 3 year period, that is 8748 € per year.	[49]	
Gastrointestinal infections	GI PCR panel	FilmArray (BioFire, bioMérieux)	Adults + infants (9402)	Cross sectional retrospective	Patients who received a GI panel were less likely to undergo any endoscopic procedure (8.4% GI panel vs. 9.6% stool culture, $p = 0.008$) or any abdominal radiology (29.4% GI panel vs. 31.7%, $p = 0.002$). Within 14 days after stool testing, patients who received a GI panel were less likely to be prescribed any antibiotic (36.2% GI panel vs. 40.9%, $p < 0.001$).	[50]
	GI PCR panel	FilmArray (BioFire, bioMérieux)	Adults + infants (241)	Single-centre retrospective	The GI panel helped decrease the need for other diagnostic tests, reducing unnecessary use of antibiotics and leading to a reduction in hospital length of stay.	[51]
Central nervous system infections	Meningitis and encephalitis	FilmArray (BioFire, bioMérieux)	Infants (145)	Multicentre prospective	FilmArray ME panel results may conduct in a decreased length of stay and in less antimicrobial exposure for infants with low-risk viral infection detected.	[52]
Malaria	Malaria testing	Illumigene Malaria (Meridian Bioscience)	Adults (298)	Multicentre retrospective and prospective	A cost-benefit analysis suggests savings of up to USD\$13 per specimen using a novel algorithm with this test.	[32]
Genital and sexually transmitted infections	HIV RNA testing (PCR)	Xpert (Cepheid)	Adults (706)	SSPS	The addition of Xpert HIV-1 Qual testing led to an increase in confirmed diagnoses by 25% (from 24 to 30 cases).	[53]
	<i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> testing (PCR)	Xpert (Cepheid)	Adults (70)	Single-centre RCT	The use of Xpert CT/NG reduced overtreatment and improved adherence.	[54]
	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> testing (PCR)	Xpert (Cepheid)	Women (254)	Single-centre RCT	Xpert CT/NG reduced overtreatment and improved undertreatment of patients tested in ED.	[55]

CI, confidence interval; ED, emergency department; GI, gastrointestinal; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; LP, *Legionella pneumophila*; mPCR, multiplex PCR; OR, odds ratio; POC, point of care; RADT, rapid antigen detection test; RCT, randomized controlled trial; SP, *Streptococcus pneumoniae*; SSPS, single-centre prospective study.

sometimes been reported to be lower than those of viral PCR [19], thus highlighting the need for caution when interpreting cumulative performance results. Furthermore, the performance of some panels only consists of percentage agreement—a strong and perhaps underappreciated limitation (Table 1).

For the diagnosis of lower respiratory tract infections in the ED, short turnaround time is a key parameter for relevant therapeutic measures when targeted treatments and specific infection prevention measures exist, as for respiratory syncytial virus or influenza [62].

Gastrointestinal infections

The rapid diagnosis of *Clostridium difficile* infection is often based on a two- or three-stage diagnostic approach using specific glutamate dehydrogenase antigen with enzyme immunoassays, amplification of toxin A/B genes by PCR and detection of toxins A/B by enzyme immunoassay (Table 1). No other enteric bacteria or virus dispose of sensitive rapid diagnostic method except for gastrointestinal multiplex PCR panels. Their performances should be considered separately for each target, and, like other syndromic panels, validation studies of some assays were performed among populations with low prevalence of certain targets, including *Vibrio* spp., *Entamoeba histolytica* and *Yersinia enterocolitica* [26]—an important consideration for interpretation of negative results.

Few data have been published on the clinical impact of RDTs for the diagnosis of gastrointestinal infections in the ED. Additional research is needed to evaluate their impact and cost-effectiveness, especially for costly but point-of-care (POC)-friendly rapid multiplex PCR assays [50,51].

Meningitis and encephalitis

Pneumococcal antigen and cryptococcal antigen detection through immunochromatographic technology are marketed to be used in cerebrospinal fluid samples, with excellent performance and short turnaround times [27].

To date, only one fully automatized rapid multiplex PCR system is available: the FilmArray ME panel (BioFire, bioMérieux), which provides results in about an hour. Common bacteria and viruses are detected, as well as the yeast *Cryptococcus neoformans/gattii* (Table 1). Performances have been evaluated retrospectively [30,63]. Both false-positive and false-negative results are possible, and thus all biological and clinical parameters should be taken into account for result interpretation, especially for uncommon targets such as *Cryptococcus* [64]. These panels are also not intended to be fully exhaustive of all possible pathogens. Finally, *Listeria monocytogenes* was not tested during the clinical validation study, necessitating specific PCR or culture if there is a high index of suspicion [30].

No data were available on the impact of RDTs on the management of patients with suspicion of meningitis/encephalitis in the ED. A retrospective analysis of 145 paediatric cases of meningitis showed that 20% of infants were discharged less than 24 hours after an enterovirus-positive result, thus highlighting some potential benefits of rapid syndromic testing [65]. Further investigation of this approach is needed, especially in adults.

Fever in the returning traveller

Malaria RDTs are critically needed for patients returning from malaria-endemic countries. Approximately 90% of cases occur in the World Health Organization African region, with *Plasmodium falciparum* being the most prevalent species, accounting for nearly all mortality. Malaria is diagnosed by three categories of tools:

expert light microscopy, immunochromatographic tests (ICTs) and nucleic acid amplification tests [66]. Light microscopy is widely used, but it requires highly trained staff. ICTs are cheap and have a sensitivity of a minimum of 95% compared to microscopy, and a specificity of >90% for all *Plasmodium* species [67]. The BinaxNOW malaria test (Alere), which is able to detect the four *Plasmodium* species, is the only ICT approved by the FDA. Currently no PCR-based RDT is commercially available. Nonetheless, a loop-mediated isothermal amplification-based molecular test (Malaria LAMP assay; Illumigene M; Meridian Biosciences) is commercially available [68]. In a prospective trial in returning travellers, this approach showed excellent analytical performance versus microscopy, with near 100% accuracy [32].

With 96 million dengue infections per year in over 100 tropical and subtropical countries in patients with nonspecific symptoms, rapid and accurate testing is important. Unfortunately, rapid ICTs detecting both NS1 antigen and immunoglobulin M have relatively low performance profiles. Their use should be limited to strong clinical suspicion, which is then confirmed by ELISA or PCR assays [33]. There is a need for multiplex testing for other arboviruses, such as Zika and chikungunya, which have resulted in large outbreaks.

Sexually transmitted infections and HIV infection

Many patients seek care at EDs for initial care of sexually transmitted infections. Point-of-care testing of sexually transmitted infections could permit the treating of cases during the initial clinical visit, thus improving adherence to treatment and further transmissions. For syphilis, available RDTs consist of lateral-flow immunoassays detecting treponemal antibodies, but they are unable to distinguish between treated and active infection, thus leading to a risk of overtreatment. However, they may be useful in resource-limited settings to avoid congenital syphilis, to reduce neonatal mortality and to decrease disease transmission [69].

Some RDT assays allow the individual or simultaneous detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, with varying performance depending on clinical specimen type (Table 1) [34,35]. Only simultaneous detection will be discussed in this review because dual testing is most clinically relevant. In the ED context, POC testing significantly decreases overtreatment of gonorrhoea and trichomoniasis compared to nucleic acid amplification testing [70]. Implementation of rapid testing for chlamydia and gonorrhoea directly from triage using self-collected specimens can markedly reduce overtreatment [34,54]. In the future, to significantly reduce the sexually transmitted infection burden, particularly for *N. gonorrhoeae* and *Mycoplasma genitalium* infections, a combination of rapid POC diagnostic and antimicrobial resistance testing will likely be needed.

Several manufacturers have also developed rapid ICTs for HIV diagnosis. Performance evaluations are generally carried out on plasma or serum samples, but not fingerstick whole-blood samples. Their use should also be cautiously implemented in the context of patients with primary infection or wide HIV diversity (HIV-1, HIV-2, HIV-O). Indeed, one study demonstrated excellent performance (sensitivity 100%, specificity >98.5%) for chronically infected patients but with inconsistent results for primary infected patients, even for tests detecting both HIV-specific antibodies and p24 antigen [39]. These tests may rarely be falsely negative among HIV-positive patients already receiving antiretroviral therapy [71,72]. Although HIV POC testing in the ED has no immediate impact on stewardship, it increases screening rates, general disease awareness and prompt referral to an HIV specialist [73].

Antimicrobial stewardship and health economics

Most EDs face overcrowding, and POC tests may facilitate discharging or admitting patients more quickly and improving ED throughput while decreasing LOS. Various clinical studies have demonstrated a significant impact on reducing antimicrobial duration when RDTs are used in the ED [54,74–76]. Conversely, other studies have failed to report such a reduction, especially in complex healthcare environments [41,43]. In this context, multidisciplinary diagnostic stewardship is essential. This refers to the appropriate use of laboratory testing to guide patient management, including treatment, in order to optimize patient outcomes and antibiotic use [77]. Indeed, implementation of new RDTs should rely on multidisciplinary approaches and high-quality evidence supporting their clinical validation and impact.

Currently there are limited data on health economic outcomes related to use of POC tests in the ED, and several of the published studies are based on simulation only [78]. Reductions in ED LOS, wait time and the number of clinic visits required to receive results were reported [79].

Work flow and implementation

Appropriate integration of RDTs into the clinical environment is often an overlooked component. Pragmatically, successful implementation depends on three key questions: Who will perform the test? What is the optimal time point of specimen collection? And where should the sample be processed? Questions on appropriate timing and who should be in charge are directly related to the ultimate goal of testing. If the primary objectives are prompt isolation (e.g. POC tests for detection of influenza in patients with influenza-like illness), quick administration of anti-infective drugs in critical patients (e.g. malaria in febrile returning traveller) or improved patient throughput testing might be performed by triage nurses on the basis of precise and simple clinical case definitions. Conversely, other tests require more complex interpretation or sampling, such as lower respiratory tract infection panels, and should thus be limited to confirmed pneumonia patients. Training for assay implementation is needed, and additional human resources may be required for timely integration into ED work flow. Clinicians also need to receive regular training on indications and interpretation of RDT results in collaboration with clinical microbiologists [80]. Finally, with the rapid expansion of RDTs in the ED for both infectious and noninfectious syndromes, space and time constraints for instruments should also be anticipated.

Conclusions

This review provides a nonexhaustive overview of currently commercially available FDA and CE RDTs for infectious diseases in the ED. Most of these assays have adequate analytical performance, but additional high-quality studies are needed to better assess their impact. These assays must be appropriately integrated into ED work flow, taking into account local constraints and priorities. Furthermore, RDTs cannot replace conventional methods because they are not exhaustive, they have performance limitations and they provide limited data on antimicrobial susceptibility profiles. Finally, and most importantly, their clinical and economic impact remains uncertain. There is a need to conduct rigorous studies, such as randomized controlled clinical trials, to determine their actual impact on clinical management and outcomes, such as time to optimal therapy, length of ED or hospital stay, cost-effectiveness and mortality, as well as their role in antimicrobial stewardship interventions.

Transparency declaration

VC reports personal fees from Accelerate Diagnostics, Astellas, bioMérieux, Correvio, Curetis, Eumédica, Menarini, Mylan, Pfizer and Sanofi. SK reports personal fees from Accelerate Diagnostics, bioMérieux and MSD. BV reports personal fees from bioMérieux and Qiagen and grant from Stat-Dx. LM reports personal fees from Cepheid, Roche, Bio-Rad and Qyella, and research grants from BioFire Diagnostics and Roche. The other authors report no conflicts of interest relevant to this article.

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Facteurs associés au placement en chambre seule des patients admis aux urgences pendant les périodes d'épidémies grippales.

Contexte et objectif

Les virus influenza sont responsables d'épidémies hivernales et représentent un problème de santé publique causant environ 650000 décès chaque année au niveau mondial [71]. Les hôpitaux doivent être vigilants pour prévenir les épidémies de grippe nosocomiale. Ses définitions sont variées, notamment pour le délai d'apparition des symptômes. Ses conséquences sont une mortalité attribuable élevée et des coûts importants en raison de l'augmentation des durées du séjour [56].

Le placement du patient grippé en chambre seule est une des pierres angulaires de la prévention des épidémies nosocomiales [72,73]. Dans une étude observationnelle prospective de 3 ans, le risque de grippe nosocomiale était 2,7 fois plus élevé chez les patients hospitalisés en chambre double, par rapport à ceux qui étaient en chambre simple [74].

Notre objectif principal était d'évaluer l'impact des résultats de la PCR réalisée au laboratoire et la gravité du patient sur le placement en une chambre seule au cours de 3 épidémies grippales successives au CHU Bichat Claude Bernard.

Méthodes

Nous avons mené une étude observationnelle rétrospective sur tous les patients testés par PCR grippale lors de trois épidémies consécutives de grippe.

Tous les patients consultant aux urgences de l'hôpital BCB à Paris, testés par PCR pour la grippe ont été inclus, quel que soit le résultat du test PCR. Nous avons secondairement exclu les patients non admis à l'hôpital BCB.

Le critère de jugement principal était l'attribution d'une chambre simple ou double au cours des 48 premières heures. Une analyse univariée et multivariée (backward) par régression logistique a été menée.

Résultats

Au total, 1330 patients ont inclus, et 278 (20,9%) ont été testés positifs pour un virus influenza en PCR. Les délais médians entre le prélèvement aux urgences et la mise à disposition du résultat de la PCR étaient de respectivement **19,3**, **19,2** et **15,7** heures pendant les trois périodes. Au total, 238 (17,8%) les patients présentant un syndrome grippal ont été placés en chambre seule ; parmi eux, 62 (26,1%) avaient une PCR positive pour un virus influenza. Lors de la troisième période, l'accès à un test de diagnostic rapide (TROD) a rendu cette épidémie non comparable, elle a donc été exclue de l'analyse multivariée.

L'attribution d'une chambre seule n'était pas associée à une PCR positive. Les facteurs associés avec l'attribution d'une chambre seule étaient le tri de niveau 1 et le fait de se présenter le week-end aux urgences. Dans l'analyse multivariée. Seul le niveau 1 de tri, selon l'échelle de l'ESI, était associé à une affectation en chambre seule (OR ajusté 1,9 ; IC à 95%, 1,3–2,8 ; $p < 0,01$), tandis qu'un résultat de PCR positif pour virus influenza n'était pas associé à cette décision (OR ajusté 1,46 ; IC à 95%, 1,0–1,9; $p = 0,07$). Les délais de rendu de résultat et les consultations durant les week-ends n'étaient plus statistiquement associés au placement en chambre seule.

Facteurs (n, %)	Placement en chambre		Analyse univariée		Analyse multivariée	
	Seule (n=223)	Double (n=697)	RR (95%CI)	p value	OR (95%CI)	p value
Age (années)* ≤ 75 (n=418) > 75 (n= 502)	93 (41,7%) 130 (58,3%)	324 (46,5%) 373 (53,5%)	1 1,2 (0,9-1,4)	0,21		
Sexe masculin (n= 476)	117 (52,5%)	359 (51,5%)	1,0 (0,8-1,3)	0,82		
PCR* Négative (n=1052) Positive (n=278)	167(74,8%) 56 (25,2%)	558 (80,0%) 139 (20,0%)	1 1,3 (0,9-1,6)	0,08	1 1,4 (1,0-1,9)	0,07
Niveau de tri* Tris 2-3-4-5 (n=771) Tri 1 (n= 149)	170 (76,3%) 53 (23,7%)	601 (86,3%) 96 (13,7%)	1 1,61 (1,2-2,1)	<0,01	1 1,9 (1,3-2,8)	<0,01
Délai de rendu de PCR* ≤6h (n=181) > 6h (n=739)	35 (15,7%) 188 (84,3%)	146 (20,9%) 551 (79,1%)	1 1,3 (0,9-1,8)	0,09		
Weekends* (n=329)	66 (29,6%)	162 (23,2%)	1,3 (1,1-1,6)	0,04		
Consultation Jour (n=647) Nuit (n=273)	155 (69,5%) 68 (30,5%)	492(70,6%) 205 (29,4%)	1 1,1 (0,9- 1,1)	0,70		

Tableau 4 Analyses univariée et multivariée des facteurs associés au placement en chambre seule au cours de trois épidémies grippales consécutives au CHU Bichat Claude Bernard

Discussion

Dans cette étude observationnelle de 3 ans, nous avons montré que la gravité des patients basée sur le niveau de tri 1 (selon l'échelle de l'ESI) était le seul facteur associé au placement en chambre seule. Seulement 25,2% des patients hospitalisés avec une PCR influenza positive ont été placés en chambre seule. Ces résultats soulignent que le placement en chambre seule du patient infecté par un virus influenza reste insuffisant, malgré le nombre de chambres seules

relativement important de notre hôpital (n=455). La principale hypothèse pour expliquer l'absence d'impact de ce résultat de PCR sur le choix de la chambre était le délai important entre le prélèvement et la mise à disposition du résultat par le laboratoire centralisé de virologie, alors que plupart des décisions médicales seront prises par l'urgentiste dans un délai bien plus court.

Notre travail présente cependant plusieurs limites dont principalement le fait que ce soit une étude monocentrique. Puis, nous n'avons pas pu récupérer le détail sur les taux d'occupation de l'hôpital et donc la disponibilité réelle des chambres individuelles est restée inconnue.

En conclusion, si le placement en chambre seule est nécessaire pour lutter contre les épidémies de grippe nosocomiale, il reste insuffisant dans les conditions décrites dans ce travail et la sévérité du malade semble être le seul facteur à influencer cette décision.

Au total, le délai médian de résultat de PCR de 18h via le laboratoire central est trop long pour être systématiquement pris en compte dans la décision médicale d'isolement en chambre seule. La proportion des patients grippés placés à bon escient en chambre seule (25%) reste très insuffisante avec ces délais. Nous n'observons pas de différence entre les tests rendu en moins de 6h par rapport aux autres délais de rendu. Nous posons donc l'hypothèse qu'un délai de rendu encore inférieur est nécessaire, mais il ne peut être atteint que par des tests de biologie délocalisée. Pour vérifier cette hypothèse, nous avons commencé par vérifier la faisabilité d'une PCR multiplex délocalisée aux urgences.

RESEARCH ARTICLE

Factors associated with single-room assignment among patients admitted through the emergency department during influenza epidemics

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Data Availability Statement: The authors are not allowed to share the data publicly as, according to French ethical laws, the raw data of epidemiological study collected as part of the medical follow-up on the framework of standard medical care cannot be shared, even anonymously, without a specific ethical committee approval. However these data are secured in our laboratory system, as required by the ISO15189 certification of our laboratory, and can be shared on request approved by an adequate ethical committee. Interested researchers may

Abstract

Introduction

Every winter, emergency departments (EDs) face overcrowding with patients presenting influenza-like symptoms, and organisational issues such as single room assignment and droplet precautions to avoid hospital-acquired influenza. Our main objective was to assess the impact of PCR results and patient's severity on single room assignment.

Methods

All patients admitted to Bichat-Claude Bernard Hospital through the ED and tested for influenza by PCR (GenXpert, Cepheid) or (FilmArray, BioMérieux) on a nasopharyngeal swab were retrospectively included during three influenza seasons (2015–2018).

Results

Of 1,330 included patients, 278 (20.9%) had a positive PCR for influenza. The median time to obtain a PCR result was 19 hours, and 238 (18.3%) patients were assigned a single room. Among patients with positive and negative influenza PCR, 22.3% and 16.7% were assigned a single room ($p = 0.03$). The multivariable analysis was performed on the two first epidemic periods, excluding the third epidemic because of the concomitant use of influenza immune-chromatic test. Only level 1 of the Emergency severity index (ESI) (aOR, 1.9; 95% CI, 1.3–2.8; $p < 0.01$) was associated with single-room assignment. PCR result was not statistically associated with the decision of single room assignment (aOR, 1.4; 95%CI, 1.0–1.4; $p = 0.07$).

submit queries related to data access to the urcest@chusa.jussieu.fr. Additionally, queries may be sent to the authors at the following email: benoit.visseaux@aphp.fr and donia.bouzi@aphp.fr.

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Abbreviations: D, Emergency department; ESI, Emergency severity index; ICU, Intensive care unit; ILI, influenza like illness; PCR, Polymerase Chain Reaction; POCT, Point of care test; RIDT, Rapid influenza diagnostic test.

Conclusion

A PCR positive for influenza was not significantly associated with single-room assignment. Less than one quarter of influenza patients were adequately assigned a single room, likely due to the long turnaround time of PCR result and other conflicting indications for single room-assignment. Accelerating biological diagnosis could improve single-room assignment.

Introduction

Influenza is a huge public health problem causing 650 000 deaths every year worldwide [1]. Annual winter epidemics of influenza also cause a large number of hospitalization, about 140,000 to 960,000 each year in the US [2], that challenge the hospital management. Though most people recover within few days, influenza can cause various and serious respiratory, cardiac or neurological complications among the elderly or other fragile patients.

During each annual winter epidemic, emergency departments (EDs) face overcrowding, with patients presenting influenza-like illness (ILI) or suspicion of pneumonia. Thus, EDs must deal with organisational issues related to patients' isolation and the risk of viral nosocomial transmission in the context of limited availability of single rooms. A study assessing the relationship between admission to double-occupancy rooms and hospital-acquired influenza showed a higher risk of acquiring influenza among patients admitted in a double-occupancy room compared to those placed in a single room [3]. In another study, the same team estimated that the hospital-acquired influenza risk was largely increased when the roommate presented an ILI [4]. Patients' isolation with single-room assignment is the cornerstone of droplet precautions along with wearing medical masks and hand hygiene [5]. However, in most settings, single rooms are rare and not available for all patients presenting an ILI. Rapid biological confirmation is thus recommended to help with isolation and single-room assignment decisions in hospital settings.

Polymerase chain reaction testing (PCR) has the highest sensitivity compared to other diagnostic tests [6–9]. However, PCR is currently mostly performed in the laboratory and has a long turnaround time, which can delay and alter single-room assignment for patients with ILI. Point of care (PoC) PCR assays decreased the time to result, hospitalisation and mortality rates [10] but without improvement regarding the proportion of influenza-positive patients correctly assigned to single rooms.

A recent study assessing the usefulness of multiplex PCR as PoC testing in the ED showed that the percentage of patients assigned to a single room among patients positive for influenza or respiratory syncytial virus was higher, although not significantly, in those with PoC testing than in those with laboratory testing, owed to a shorter PCR turnaround time (37.1 vs 2.3 hours) [11]. As in other studies assessing PoC usefulness [10,12,13], this study did not assess for the potential others factors possibly involved in room assignment.

Our main objective was to assess the association of influenza PCR and disease severity on single-room assignment, during the first 48 hours of admission, for patients seeking the ED during influenza epidemics.

Methods

We conducted a retrospective study at the ED of Bichat-Claude Bernard university Hospital. This is a tertiary hospital in Paris, serving a population of more than 350,000 inhabitants. The

ED receives more than 80,000 visits per year. The hospital includes 455 single rooms and 276 double rooms.

All patients admitted to the hospital through the ED and tested for influenza PCR during three consecutive influenza epidemics between 2015 and 2018 were included. During the study period, two PCR were used: GenXpert[®] (Cepheid, Sunnyvale, CA, USA) or FilmArray[®] RP panel (BioFire[®], BioMérieux, Marcy-L'Étoile, France). All PCR assays were performed in the virology laboratory during opening hours (8 a.m. to 6 p.m. from Monday to Friday, and 8 a.m. to 1 p.m. on Saturday).

The definition of influenza epidemic periods was based on the French national surveillance system [14]. According to the national surveillance system, the first epidemic period extended from 25 January 2016 to 17 April 2016, the second from 5 December 2016 to 12 February 2017, and the third from 4 December 2017 to 17 April 2018.

Virological data were extracted from the virology laboratory database and merged with the ED database, containing clinical data, and to the medical information system, containing duration of hospital stay and room assignment. Variables included demographic characteristics, level of triage according to the Emergency Severity Index (ESI) (ranging from 1 requiring immediate, life-saving intervention without delay to 5 meaning stable, without any resources anticipated except oral or topical medications, or prescriptions) [15,16], PCR turnaround time, ward of admission, and room assignment.

The primary outcome was the single- or double-room assignment at 48 hours of hospital stay, whatever the type of unit of stay, either a clinical ward or the downstream ED unit.

Variables were summarised as frequency and proportion for categorical variables and median and interquartile range for continuous variables. Continuous variables were converted into categorical variables using their interquartile range. We compared the characteristics of the three epidemics using the Kruskal-Wallis test for quantitative variables and the χ^2 test for the qualitative variables. Logistic regression was used to identify factors influencing the primary outcome in the multivariable analysis including: age, PCR results, weekend shifts, time between ER sampling and PCR results. During the third period, ED physicians used a point of care testing with an immune-chromatographic method in addition to PCR, therefore shifting the association between time to PCR results and room assignment. All tests were performed with a type I error of 0.05. The data management and statistical analysis were performed using Stata15[®].

The study design has been approved by the Bichat Claude Bernard ethic committee (N° 2019–029).

Results

Among the 2563 patients, 1233 were not included because they were previously included in the study or not admitted after their visit at the ED. Thus, we included 1330 patients: 319, 601, and 410 during the first, second, and third epidemic period, respectively (Fig 1). A total of 278 patients (20.9%) tested positive for influenza with PCR.

The sex ratio was similar across the three periods; several differences were observed (Table 1). Patients were younger during the first period than during the second and third periods ($p < 0.001$); only influenza type A virus was identified during the second period, while both influenza A and B were detected during the first and third periods; the triage level distribution was also significantly different over the three periods ($p = 0.02$); however, the proportion of level-1 triage, representing the 221 most severe patients (16.6%) with either hemodynamic or respiratory failure was not statistically significant among the three periods ($p = 0.49$). Finally, the distribution of ward admission was significantly different between, with

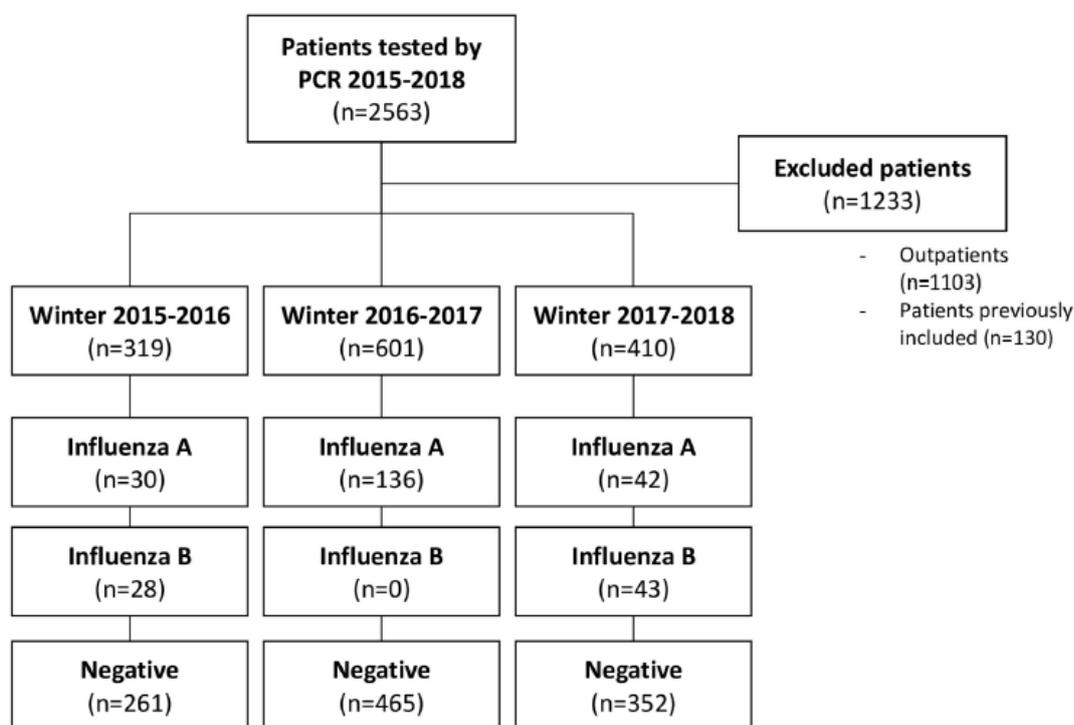


Fig 1. Study flowchart.

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more patients admitted to a surgical ward during the second period as compared to the first and third periods. Overall, 36 (2.7%) patients were admitted to the intensive care unit (ICU) from the ED.

The median turnaround times between ED sampling and PCR result were 19.3, 19.2, and 15.7 hours during the first, second, and third period, respectively (Table 2). In total, 238 (17.8%) patients were assigned to a single room within the first 48 hours after admission. Among those 238 patients with IL assigned a single room, 62 (26.1%) had a positive PCR.

During the third epidemic, ED physicians had access to an influenza point of care test, which made this epidemic not comparable to the other epidemic. Indeed we observed an interaction between this third period and PCR turnaround time, therefore we have chosen to exclude the third epidemic from the logistic regression analysis. There was no association between single-room assignment and positive PCR result (Table 3). The only factors associated with single-room assignment in the univariable analysis were the level-1 triage and weekend visits to the ED. We did not observe statistically significant difference between day or night visits and the type of room assignment.

In the multivariable analysis. Only level 1 of triage according to ESI was associated to single-room assignment (adjusted OR, 1.9; 95% CI, 1.3–2.8, $p < 0.01$), while a positive PCR result for influenza was not (aOR, 1.46; 95% CI, 1.0–1.9; $p = 0.07$); turnaround time and weekends were no longer statistically associated to single-room assignment.

Table 1. Characteristics of included patients with ILI, during the three winter epidemics (2015–2018) at Bichat Claude Bernard Hospital.

Characteristics (n, %)	Winter 2015–2016 (319 patients)	Winter 2016–2017 (601 patients)	Winter 2017–2018 (410 patients)	p value
	(n,%)	(n,%)	(n,%)	
Gender				0.76
Female (n = 629)	147 (46.1)	297 (49.4)	185 (45.2)	
Male (n = 701)	172 (53.9)	304 (50.6)	225 (54.8)	
Age (years, median, IQR)	73.9 (61.2–82.6)	79.6 (66.6–87.7)	77.4 (64.2–87.9)	<0.001
< 65 (n = 346)	96 (30.1)	139 (23.1)	111 (27.1)	
65–75 (n = 259)	73 (22.8)	110 (18.3)	76 (18.5)	
76–85 (n = 310)	82 (25.7)	136 (22.6)	92 (15.3)	
> 85 (n = 415)	68 (21.3)	216 (35.9)	131 (31.6)	
Triage level:				0.01
Level 1 (n = 221)	50 (15.7)	99 (16.5)	72 (17.5)	
Level 2 (n = 377)	104 (32.6)	147 (24.5)	126 (30.7)	
Level 3–4–5 (n = 732)	165 (51.7)	355 (59.1)	212 (51.7)	
Ward admission				<0.001
Medical (n = 942)	236 (73.9)	393 (65.4)	313 (76.3)	
Surgical (n = 156)	22 (6.9)	93 (15.4)	41 (10)	
ICU (n = 36)	11 (3.4)	13 (2.1)	12 (2.9)	
Transferred (n = 196)	50 (15.7)	102 (16.9)	44 (10.7)	

Abbreviations: PCR, Polymerase Chain Reaction; IQR, Inter Quartile Range.

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Discussion

In this 3-year observational study in a large teaching hospital, we showed that patients' severity based on ESI level 1 was the only factor associated with single room. Only 25.2% of admitted patients presenting a positive PCR for influenza were assigned to a single room. These results underline that patient's isolation remains insufficient, despite a large number of 455 single rooms in our hospital.

Previous studies have shown that single-room assignment is efficient in reducing nosocomial infections, specifically influenza [17,18], but the availability of single rooms is often still beyond the needs during influenza seasons [19]. Despite the fact that newly built hospitals may

Table 2. Summary of PCR results and room assignment for patients with ILI during the three winter epidemics (2015–2018), at Bichat Claude Bernard Hospital.

Characteristics (n, %)	Winter 2015–2016 (n = 319)	Winter 2016–2017 (n = 601)	Winter 2017–2018 (n = 410)	p value
Positive PCR (n = 278)	58 (18.2)	136 (22.6)	85 (21.2)	
Influenza A (n = 208)	30 (51.7)	136 (100)	42 (49.4)	<0.001
Influenza B (n = 71)	28 (48.27)	0 (0)	43 (50.5)	
Time between sampling and PCR result (hours, median, interquartile range)	19.3 (7.2–36.6)	19.2 (9.7–29)	15.6 (4.8–27.4)	
≤ 6 h	71 (22.2%)	110 (18.3)	134 (32.7)	<0.001
> 6h	248 (77.8%)	491 (81.7)	476 (67.3)	
Room assignment				
Single room (n = 238)	82 (25.7)	141 (23.5)	15 (3.6)	<0.001
Double room (n = 1092)	237 (74.3)	460 (76.5)	395 (96.4)	

Abbreviations: PCR, Polymerase Chain Reaction; IQR, Inter Quartile Range.

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Table 3. Univariable and multivariable analysis of factors associated with a single room assignment for patients with ILI during two winter epidemics (2015–2017) at Bichat Claude Bernard hospital.

Factors (n, %)	Room assignment		Univariable analysis		Multivariable analysis	
	Single (n = 223)	Double (n = 697)	RR (95%CI)	p value	OR (95%CI)	p value
Age (years)*				0.21		
≤ 75 (n = 418)	93 (41.7%)	324 (46.5%)	1			
> 75 (n = 502)	130 (58.3%)	373 (53.5%)	1.2 (0.9–1.4)			
Male gender (n = 476)	117 (52.5%)	359 (51.5%)	1.0 (0.8–1.3)	0.82		
PCR*						
Negative (n = 1052)	167 (74.8%)	558 (80.0%)	1		1	
Positive (n = 278)	56 (25.2%)	139 (20.0%)	1.3 (0.9–1.6)	0.08	1.4 (1.0–1.9)	0.07
Triage level*						
Level 2-3-4-5 (n = 771)	170 (76.3%)	601 (86.3%)	1		1	
Level 1 (n = 149)	53 (23.7%)	96 (13.7%)	1.61 (1.2–2.1)	<0.01	1.9 (1.3–2.8)	<0.01
ER sampling to PCR results*						
≤6h (n = 181)	35 (15.7%)	146 (20.9%)	1			
> 6h (n = 739)	188 (84.3%)	551 (79.1%)	1.3 (0.9–1.8)	0.09		
Weekends* (n = 329)	66 (29.6%)	162 (23.2%)	1.3 (1.1–1.6)	0.04		
Type of shift						
Day (n = 647)	155 (69.5%)	492 (70.6%)	1			
Night (n = 273)	68 (30.5%)	205 (29.4%)	1.1 (0.9–1.1)	0.70		

Abbreviations: PCR, Polymerase Chain Reaction.

* Included in multivariable analysis.

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tend to include larger numbers of single rooms [20], the placement of patients with high-risk respiratory viral infection, notably influenza infection, remains a challenge. In addition, the proportion of influenza infections is usually low among patients presenting an ILI during outbreak periods, about 20% in our study and in previous works [21,22]. Thus, a rapid virological diagnosis is required to appropriately decide which patient with ILI should be assigned to an available single room. However, we did not find an association between the time to result, defined as the delay between ED sampling and PCR results, and single-room assignment. This may be largely explained by a minimal time to result in our study always being longer than 3 hours due to sample transportation to the laboratory and PCR delay. Due to these delays and the limited opening hours of the laboratory, the median time to result was 19 hours. This might remain too long to allow the consideration of the result by the ED physician at the decision-making time. This is in line with a recent randomised study that showed that performing influenza PoC PCR improved the proportion of patients isolated with a confirmed respiratory virus infection (17 vs 9%, $p = 0.02$) and reduced the hospital length of stay [11]. Furthermore, in a post-hoc analysis, the same authors showed that a PCR result obtained in less than 2 hours reduced the duration of antibiotic treatment by half and reduced the length of hospital stay by about 3 days [23]. Further studies are required to evaluate the impact of PoC influenza PCR and placement in single rooms.

In the current work, single-room assignment was associated with patient severity, defined as level-1 triage of the ESI. It has been shown that severe patients have a longer length of stay in the ED [24], but no previous study has assessed the impact of the ESI on single-room assignment in the downstream unit.

To our knowledge, our study is the first to assess factors leading to single-room assignment in adult patients presenting an ILI. Due to the study's retrospective and observational design, our results reflect the actual practice in a French ED and contrast with a recent study [11]. As any patient presenting with ILI is required to be placed in a single room pending PCR result, our low proportion of influenza-positive patients in single room was surprising and highlight the difficulties of such organization in the emergency context.

Our work presents several limitations. Firstly, it was a retrospective and monocentric study. During the study period, several changes occurred in the global management of patients presenting an ILI, especially during the third epidemic period: a new multiplex PCR was available and allowed faster results, with a median turnaround time of 15.6 vs 19.3 hours for the previous epidemics. In addition, a new algorithm for the influenza diagnosis based on an immuno-chromatographic rapid influenza diagnostic test (RIDT) was applied in the ED at the same period, in parallel to the PCR testing at the virology laboratory. Based on this algorithm, all patients presenting an ILI were initially tested using a PoC RIDT; only patients admitted in the hospital were tested by a PCR in the virology laboratory. The observed poor accuracy of the RIDT might explain the lower frequency of single-room assignment of patients with a positive PCR. Excluding the third epidemic period, the proportion of patients with positive PCR assigned a single room was higher, at 24%. This distinct period also illustrates that single room assignment for influenza-positive patients remains a year to year challenge that could not be resolved by a rapid but less reliable PoC method. Secondly, we could not retrieve the detailed occupancy rates during the epidemics, and the actual availability of single rooms remained unknown. This parameter should, intuitively, also be linked to single-room assignment. We also did not know if some influenza positive patients may have been rarely cohorted in double rooms. Finally, the ED database lacked information for two critical time points: the time of decision for hospital admission and the time of actual information of the ED physician of the PCR result. The proportion of patients with a positive influenza PCR assigned to a single room remained low over the three periods. However, in a 2018–2019 pilot study conducted in our ED with a Multiplex PCR point of care method, allowing a result within one hour, 80% of patients were assigned to a single room [25]. Taken together with the result of the current study, this suggests that PCR turnaround time should be greatly shortened for decision making of room assignment.

Conclusion

Hospital-acquired influenza is an old and well-known threat that the physicians must tackle by applying preventive measures based on accurate and rapid diagnosis. The optimal protocol to optimise both costs and patient isolation management is yet to be precisely identified. Our results highlighted that a large majority of influenza-positive patients were still assigned double-occupancy rooms and it is likely due to the long turnaround time of PCR results. As most ED physician decisions are made in a data frame of a few hours, shortening the time to result by implementing point of care PCR should improve patients' management, facilitate the ED organisation, and improve isolation and droplet precautions during the overcrowded influenza season.

Supporting information

S1 File.
(DOCX)

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Implémentation d'une PCR multiplex dans un service d'accueil des urgences

Contexte et objectif

Compte tenu des conclusions contradictoires des quelques études évaluant l'usage de la PCR multiplexe délocalisée aux urgences, nous avons voulu évaluer l'impact de cette approche dans le contexte du service d'accueil des urgences de notre CHU. Nous avons conduit une étude de faisabilité lors de la période d'épidémie grippale 2018-2019 et comparé quelques mesures d'impact, surtout le placement en chambre seule, avec les données historiques relevées dans l'étude précédente.

Méthodes

Il s'agissait d'une étude prospective de faisabilité, monocentrique, conduite dans le service d'accueil des urgences au cours de l'épidémie grippale de l'hiver 2018-2019. La PCR multiplex QIAstat-Dx respiratory panel (Qiagen®) a été mise en place aux urgences. Ce panel permet le diagnostic de plus de 23 pathogènes respiratoires avec un délai de réponse de 67 minutes. Ce dispositif fonctionne sur des prélèvements nasopharyngés par introduction directe de l'écouvillon dans la cartouche.

Sept médecins urgentistes ont été formés à l'usage de cette PCR. Ces critères d'inclusion étaient les suivants : tout patient présentant un syndrome grippal selon la définition de l'eCDC et qui étaient triés en niveau 1 ou 2 sur l'échelle de l'ESI (patients les plus sévères aux urgences). Ces patients bénéficiaient alors d'un prélèvement nasopharyngé technique directement sur la PCR installée dans la salle de déchocage.

Résultats

166 patients atteints de syndrome grippal ont été testés par mPCR aux urgences. Neuf tests ont échoué (5%) et ces patients ont été exclus de l'analyse.

L'âge médian des 157 patients était de 72 ans, avec un peu plus d'hommes que de femmes (89 hommes, 56%). Le taux de positivité du mPCR était de 50% (79/157), avec six co-infections. Les virus influenza A, le rhinovirus et les VRS ont été identifiés parmi 46 (58%), 12 (15%) et 12 (15%) des 79 échantillons positifs, respectivement. Aucune différence significative dans les symptômes n'a été observée entre les groupes. Respectivement 37 sur 49 (80%), 24 sur 37 (65%) et 32 sur 78 (41%) patients avec une PCR influenza positive, ou une PCR positive à un

autre pathogène respiratoire ou une PCR négative se sont vu attribuer une chambre individuelle ($p < 0,001$). Presque tous les patients avec une PCR positive à un virus influenza (45/46, 98%) ont reçu de l'oseltamivir, versus six patients sur les 111 (5%) qui n'avaient pas ces virus ($p < 0,001$). Vingt sur 46 (43%) patients influenza positifs et 39 sur 111 (35%) influenza négatifs ont reçu un traitement antibiotique empirique ($p = 0,46$).

Discussion

Ce travail a montré que la mise en place d'une mPCR dans un service d'accueil des urgences est faisable avec un temps de formation raisonnable, un faible taux d'échec des tests et un taux de positivité très satisfaisant. Les indications ont été bien respectées et le test a permis une meilleure utilisation du traitement antiviral chez les patients porteur de virus influenza et, surtout a conduit à une attribution de chambre seule pour ces malades dans 80 % des cas. Pour rappel, l'étude rétrospective conduite dans le même établissement et décrite plus haut avait montré qu'uniquement 25 % des patients grippés se retrouvaient hospitalisés dans une chambre seule lorsque testé au laboratoire spécialisé. Néanmoins cette étude présente différentes limites, elle est monocentrique, les patients n'ont été suivis que lors de leur 48 premières heures d'hospitalisation.

L'adéquation de placement en chambre seule en fonction de leur infection par les virus influenza (80%), le VRS (75%) ou le métapneumovirus (75%), pour lesquels les recommandations locales de notre CHU demandent un placement en chambre seule, et une meilleure prescription antivirale sont des résultats qui encouragent le recours à la mPCR aux urgences.

Au total, l'intégration de la PCR multiplex au sein d'un service d'accueil des urgences s'est révélée simple de mise en œuvre, ne s'est pas accompagnée d'un non-respect des indications, ni d'incidents techniques complexes. Nous avons montré que cette PCR multiplex délocalisée permet de mieux guider le placement en chambre seule des patients infectés par les virus influenza et d'instituer un traitement antiviral adapté. Pour vérifier ces impacts bénéfiques et compléter par l'étude des impacts sur l'antibiothérapie et la durée de séjour, nous avons mis en place un essai pragmatique prospectif évaluant l'impact de la PCR multiplex délocalisée aux urgences sur la prise en charge des patients suspects de pneumonies.



Letter to the Editor

Multiplex PCR implementation as point-of-care testing in a French emergency department



Sir,

The increasing availability of syndromic testing for respiratory infections allows identification of almost all respiratory viruses, and some bacteria, involved in influenza-like illness (ILI) [1]. US guidelines specifically recommend use of influenza and multiplex polymerase chain reaction (mPCR) if these can change the management of hospitalized patients [2]. Patient benefit relies on rapid turnaround of results; in this regard, several kits are suitable for point-of-care (POC) use [3–5]. A few studies have investigated the impact of these tests on anti-infective prescribing, their potential cost-effectiveness and length of stay [3,5]. However, to the authors' knowledge, no studies have focused on the impact of mPCR on infection prevention measures such as droplet precautions and single-room allocation of hospitalized patients.

As such, we conducted a prospective feasibility study of the use of mPCR as a POC test in the Emergency Department (ED) of our 850-bed hospital during the 2018–2019 influenza epidemic season. The impact of mPCR use on single-room assignment and antiviral use among patients seeking care in the ED was evaluated.

mPCR has been performed for all admitted patients seeking emergency care for ILI or pneumonia since 2015. During the 2018–2019 influenza season (mid-December 2018 to mid-March 2019), a rapid mPCR method with a turnaround time of 67 min was implemented as a POC test in the ED (QIA-Stat Dx RP2 panel; Qiagen, Hilden, Germany). Seven emergency physicians were trained to perform the mPCR test on nasopharyngeal swabs of all patients with ILI symptoms and with a triage level of 1 or 2 according to the Emergency Severity Index (ESI) [6]. Data on demographic characteristics, level of triage (ESI), antibiotic and antiviral prescriptions, ward of admission and room assignment were collected prospectively. Statistical analysis was performed using Stata Version 15 (Stata Corp., College Station, TX, USA). The research was approved by the local ethics committee (CEERB N2019-050).

During the study period, 166 patients with ILI were tested by mPCR in the ED. Nine had a failed test (5%) and were excluded from the analysis. The median age of the 157 included patients was 72 years, with slightly more men than women ($N = 89$, 56%). The positivity rate of mPCR was 50% (79/157), including

six co-infections. Influenza A, rhinovirus and respiratory syncytial virus (RSV) were identified in 46 (58%), 12 (15%) and 12 (15%) of the 79 mPCR-positive samples, respectively (Table 1). Among influenza-positive patients, fever, shortness of breath, cough and myalgia were present in 31 (67%), 40 (87%), 39 (85%) and 20 (43%), respectively. Fever was present in 17 (51%) patients with viruses other than influenza, and in 26 of 78 (33%) patients who were mPCR-negative. No significant differences in symptoms were observed between groups. Thirty-seven of 49 (80%), 24 of 37 (65%) and 32 of 78 (41%) patients with influenza-positive, non-influenza-positive and negative mPCR were assigned a single room, respectively (Table 1). The difference was significant ($P < 0.001$). Nearly all influenza-positive patients (45/46, 98%) received oseltamivir, contrasting with six of 111 (5%) non-influenza patients ($P < 0.001$). Twenty of 46 (43%) influenza-positive patients and 39 of 111 (35%) non-influenza patients received empirical antibiotic treatment ($P = 0.46$). The median length of stay of patients with a positive mPCR was 3 days, 34 of 79 (43%) were admitted to the intensive care unit and eight (5%) died during the hospital stay, without differences according to the pathogen.

In a large French ED using a POC mPCR testing strategy, patients with influenza received appropriate antiviral treatment in nearly all instances, and were assigned a single room in 80% of cases, as well as 75% of cases of the two other most severe viruses, RSV and metapneumovirus. A previous retrospective study conducted in the study ED showed that, with a median laboratory mPCR turnaround time of 19 h, only 22% of patients with influenza were appropriately assigned to a single room. Non-isolation of influenza-positive patients in a single room can be due to multiple reasons, including the variable epidemic course and the local availability of those rooms. Until now, a few studies had assessed the impact of a rapid turnaround time for multiplex testing. Most agreed on a global benefit despite their cost ranging from 80 to 140 € per unit [3–5,7]. A recent study in England showed a reduction of £64 per stay, and another study in China showed a reduction of US\$200 per stay [3,5]. However, these two studies did not provide a clear description of any improvement in utilization of isolation facilities. Among the limitations, the present study was undertaken in a single centre with a limited number of patients. Patients were followed until transfer to clinical wards, whereupon the impact of mPCR on antibiotic duration or cost-effectiveness could not be evaluated. However, the high mPCR positivity rate, and the low failure rate, point to correct use of the test by a relatively small number of trained ED physicians. High rates of assignment to single rooms for patients with the most severe viruses, and appropriate use of antiviral treatment strongly suggest the benefits of POC mPCR

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Table I

Distribution of patient management and follow-up according to multiplex polymerase chain reaction (mPCR) results

mPCR results (N=157)	Single room	Double room	Antibiotic treatment	Treatment with oseltamivir	ICU admission	Length of stay (days), median (IQR)
Negative (N=78)	32 (41%)	46 (59%)	23 (29%)	2 (2%)	12 (15%)	2 (1–8)
Influenza A (N=46 ^a)	37 (80%)	9 (19%)	20 (44%)	45 (98%)	17 (21%)	3 (1–7)
RSV (N=12 ^b)	9 (75%)	3 (25%)	5 (42%)	3 (25%)	1 (11%)	2 (1–8)
Rhinovirus (N=12)	6 (50%)	6 (50%)	3 (33%)	1 (11%)	10 (22%)	3 (2–9)
Others (N=9 ^c)	7 (78%)	2 (22%)	8 (88%)	0 (0%)	6 (66%)	6 (0–23)

ICU, intensive care unit; RSV, respiratory syncytial virus; IQR, interquartile range.

^a Including two codetections with RSV and two with a coronavirus.^b Including one codetection with a rhinovirus.^c Including two coronaviruses, three *Mycoplasma pneumoniae* and four human metapneumoviruses.

testing. Additional studies are needed to confirm the clinical impact and cost-effectiveness of this approach, as well as the benefits on isolation management of syndromic testing as a POC method in the ED setting.

Conflict of interest statement

None declared.

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Un essai clinique contrôlé évaluant la valeur ajoutée des tests syndromiques respiratoires rapides réalisés aux urgences versus au sein d'un laboratoire de biologie

Contexte et objectif

Parmi les agents pathogènes responsables de la pneumonie et des infections respiratoires, le rôle des virus a récemment été mis en évidence par l'émergence des tests syndromiques [75].

D'autre part, la sur-prescription des antibiotiques joue un rôle important dans l'augmentation de la résistance bactérienne aux antibiotiques, il est donc essentiel de documenter rapidement l'agent responsable des infections des voies respiratoires basses et de décider si un traitement antibiotique est nécessaire ou doit être poursuivi.

Les tests de diagnostic syndromique rapide (<2 heures) se sont beaucoup développés au cours des dernières années [59]. Les directives de la société américaines de maladies infectieuses ou IDSA ont récemment inclus la PCR multiplex (mPCR) pour prendre en charge les patients atteints d'infections des voies respiratoires basses qui nécessitent une hospitalisation, immunodéprimés ou non, même si les bénéfices réels semblent encore peu évalués [76].

Plusieurs études récentes ont étudié ces impacts de la mPCR délocalisée. Certains résultats sont contradictoires, mais deux ont montré des réductions substantielles des durées d'hospitalisation, avec une diminution de l'utilisation des antibiotiques [38,40,41]. Cependant, une limite de ces deux études c'est qu'elles comparent souvent l'utilisation de tests syndromiques mPCR en POCT à l'utilisation dans des laboratoires centralisés d'une approche plus classique incluant le diagnostic systématique des virus influenza mais pas des autres virus respiratoires. Les impacts des mPCR délocalisées sur le placement en chambre seule sont peu étudiés.

Nous avons mené une étude prospective monocentrique, quasi-randomisée, pour mesurer l'impact de l'utilisation des tests syndromiques rapides en POCT aux urgences comparés à leur utilisation au laboratoire central.

Méthodes

Nous avons réalisé une étude prospective monocentrique quasi expérimentale, pragmatique et prospective au service des urgences de notre CHU, à Paris.

La conception de l'étude comprenait des périodes alternées hebdomadaires. Au cours de la période POCT (semaine A), le test mPCR a été effectué aux urgences 24 heures/24, 7 jours/7.

Pendant la période du laboratoire central (semaine B), ces tests mPCR ont été effectués dans le laboratoire central de virologie de l'hôpital.

Les patients ont été inclus durant la période hivernale 2019-2020, du 19 novembre 2019 au 9 mars 2020. Cette dernière date correspond à l'émergence de la pandémie COVID-19 et à la recommandation nationale française de réaliser le dépistage systématique du SARS-CoV-2 chez les patients admis à partir d'un service d'urgence.

Les patients inclus étaient des adultes (âgés de > 18 ans) présentant des symptômes compatibles avec une infection respiratoire selon la définition du syndrome grippal (*ILI*) du centre européen de prévention et de contrôle des maladies (*eCDC*) et nécessitant une hospitalisation quelle que soit la sévérité des symptômes.

Pour le test des virus respiratoires, nous avons utilisé le QIAstat-Dx Respiratory Panel V2 (Qiagen, Hilden, Allemagne). Cf l'article pour les cibles du panel.

Le critère de jugement principal retenu était la durée du séjour à l'hôpital (LOS). Les critères de jugement secondaires étaient la proportion de durées de séjour aux urgences (ED-LOS) <1 jour, la prescription d'antibiotiques et l'affectation des patients à une chambre simple ou à une chambre double avec un lit bloqué.

Les analyses statistiques

La taille de l'échantillon a été calculée en fonction du critère de jugement principal, c'est à dire une réduction de la durée de séjour de 2 jours, une puissance de 90% et un risque α de 5%. Ainsi, le nombre de sujets requis était de 518, avec 259 patients par bras. Nous avons utilisé une régression linéaire pour le critère de jugement principal LOS et rapporté une différence moyenne avec un intervalle de confiance à 95% à partir d'une analyse univariée. Le modèle multivarié incluait le sexe, l'âge et le niveau de tri selon l'échelle de ESI comme covariables. Une régression logistique a été réalisée pour l'analyse de l'impact du test délocalisé sur le nombre de durée de séjour dans le service d'urgence inférieur à 1 jour et l'attribution d'une chambre individuelle ou double avec un lit bloqué. Les (OR) et l'intervalle de confiance (IC) à 95% sont indiqués en utilisant une approximation normale=

Résultats

Au total 525 patients ont été inclus au cours de la période d'étude, dont 48 ont été exclus (sortis sans hospitalisation) et 13 ont été exclus (critères d'inclusion non remplis). Les caractéristiques des patients dans les deux bras étaient similaires. L'âge médian était de 73 ans [IQR: 62-85], avec une majorité d'hommes (56%, n = 266). Entre les deux bras, les patients n'avaient pas de différences statistiquement significatives dans la présentation clinique initiale.

Le temps de rendu médian pour les résultats de mPCR était respectivement de 1,1 heure [IQR: 1,1-1,1] et 19,6 heures [IQR: 12,7-39,2] dans le bras POCT et le bras laboratoire centralisé (p <0,001). Un total de 186 (39,2%) patients ont eu une PCR positive pour au moins un pathogène respiratoire, dont 13 (3%) cas de co-détection de pathogènes. Les agents pathogènes identifiés comprenaient 55 virus influenza (30%), 54 HRV (30%), 30 VRS (15%), 23 hMPV (12%), 19 coronavirus humains (10%), 11 parainfluenza (6%), 3 *Mycoplasma pneumonia* (2%), 1 *Legionella pneumophila* (1%) et 1 bocavirus (1%). Aucune différence statistiquement significative n'a été observée entre les bras dans la distribution des agents pathogènes.

La durée de séjour hospitalière n'était pas différente entre les deux bras, avec une différence moyenne ajustée en fonction du sexe et de l'âge de 0,3 jours supplémentaire dans le bras POCT (IC à 95%, -1,2–2,8; p = 0,66).

Les proportions de patients avec une durée de séjour aux urgences inférieure à un jour n'étaient pas significativement différentes entre les deux bras (Tableau 3). Aucune différence n'a été observée entre les deux bras pour la durée du traitement antibiotique, le nombre de prescription d'antibiotiques ou le service d'admission.

Les patients du bras POCT étaient plus fréquemment placés en chambre seule lorsqu'ils avaient une PCR positive pour les pathogènes suivants : virus influenza, VRS et métapneumovirus (52/70 (74%) dans le bras POCT versus 19/38 (50%) dans le bras central bras de test. L'analyse multivariée a confirmé ces associations entre les tests POCT et l'attribution d'une chambre seule (OR, 2,9; IC à 95%, 1,3–6,8; p = 0,014). (Tableau 5).

	Placement en chambre seule au cours des semaines laboratoire n/N (%)	Placement en chambre seule au cours des semaines POCT n/N (%)	P value*
Placement en chambre seule	82/199 (41)	119/275 (43)	0.72
Placement en chambre seule pour Influenza, VRS et metapneumovirus	19/38 (50)	52/70 (74)	0.019
Influenza A	8/14 (57)	27/35 (77)	0.18
Influenza B	1/2 (50)	4/4 (100)	0.33
Metapneumovirus	1/7 (14)	11/16 (69)	0.027
RSV	9/15 (60)	10/15 (67)	1
Placement en chambre seule inutile au regard du pathogène détecté ou de son absence	66/161 (40)	70/205 (34)	0.36
Rhinovirus	8/19 (42)	7/28 (25)	0.34
Parainfluenza	2/3 (67)	2/8 (25)	0.49
Coronavirus	2/3 (67)	8/13 (62)	1
PCR négative	53/133 (40)	53/155 (34)	0.33

Tableau 5 Placement en chambre seule en fonction du pathogène détecté à la PCR multiplex

Discussion

Cet essai contrôlé prospectif, pragmatique et quasi-randomisé, a comparé l'impact d'une approche utilisant systématiquement le recours à la PCR multiplex des pathogènes respiratoires (mPCR) réalisée en tant que test délocalisé aux urgences (POCT) ou effectuée dans le laboratoire centralisé de virologie. Le délai médian de résultat est passé de 19,6 heures dans le bras laboratoire central à 1,1 heure dans le bras POCT.

Ainsi l'utilisation délocalisée d'une mPCR n'a pas raccourci la durée de séjour hospitalière ni réduit la prescription des traitements antibiotiques. Cependant, elle a montré une meilleure adhésion aux recommandations de prévention du risque infectieux grâce à une meilleure attribution de chambres seules aux patients porteurs d'un virus d'intérêt qui passe de 50% dans le bras laboratoire central à 74% dans le bras POCT (P = 0,019) pour les virus influenza, VRS et métapneumovirus.

Nos résultats apparaissent quelques peu contradictoires avec les deux études précédentes sur les mPCR délocalisées[38,41]. En effet, contrairement à ces dernières, on ne montre pas de réduction de la durée de séjour hospitalière ni de prescription d'antibiotiques. Néanmoins ces

études comparaient la mPCR en POCT versus des PCR influenza au laboratoire non systématiquement complétées pour les autres virus respiratoires.

L'impact positif sur le placement en chambre seule est cependant un résultat important et d'autant plus d'actualité du fait de la pandémie actuelle de SARS-CoV-2 avec la nécessité de placement en chambre seule.

Notre étude a plusieurs limites. Premièrement, il s'agit d'une étude monocentrique menée dans un centre ayant une expérience préalable des tests mPCR. Deuxièmement, en raison de l'objectif de l'étude, il n'a pas été possible de réaliser une étude en aveugle du groupe de randomisation POCT ou laboratoire centralisé. Troisièmement, l'utilisation de périodes hebdomadaires successives peut ne pas être idéale car la situation épidémiologique peut changer d'une semaine à l'autre. Cependant, l'alternance des semaines limite ces effets et nous n'avons pas observé de distributions significativement différentes de patients ou d'agents pathogènes entre les deux périodes.

En conclusion, l'utilisation des mPCR délocalisées pour les adultes atteints d'un tableau respiratoire aigu pendant les périodes d'épidémies grippales et consultant aux urgences n'a pas permis de réduire la durée de séjour hospitalière ni la prescription d'antibiotiques. Néanmoins, cette approche a été associée à une augmentation significative de l'attribution de chambre seule chez les patients positifs pour un pathogène respiratoire nécessitant le placement en chambre seule.

Au total, le recours à la mPCR aux urgences permet un placement en chambre seule bien plus adapté des patients infectés par des virus à haut risque pathogène. Cependant le seul recours à cette mPCR ne suffit pas pour avoir un impact sensible sur la durée de séjour et sur la prescription des antibiotiques. Des approches combinées, ajoutant par exemple la procalcitonine et le scanner thoracique au résultat de la mPCR, sont à évaluer pour améliorer ces aspects. Du fait de l'interruption précoce de l'étude RespiFast2, liée à l'émergence du SARS-CoV-2, Nous nous sommes intéressés dans la suite aux caractéristiques cliniques de cette nouvelle pneumonie virale.

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1 **Added value of rapid respiratory syndromic testing at point of care vs central**
2 **laboratory testing: a quasi-randomized control trial**

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23

24 **Synopsis**

25 *Background*

26 Virus-associated respiratory infections are in the spotlight with the emergence of SARS-CoV-
27 2 and the expanding use of multiplex PCR (mPCR). The impact of molecular testing as a
28 point-of-care test (PCOT) in the emergency department (ED) is still unclear.

29 *Objectives*

30 We aimed to compare the impact of a syndromic test performed in the ED as a POCT and in
31 the central laboratory on length of stay (LOS), antibiotics use and single-room assignment.

32 *Patients/materials and methods*

33 From 19 November 2019 to 9 March 2020, adults with acute respiratory illness seeking care
34 in the ED of a large hospital were enrolled, with POCT performed in the ED (week A) or at
35 the central laboratory (week B).

36 *Results*

37 Of 525 enrolled patients, 474 could be analyzed: 275 during A weeks and 199 during B
38 weeks. Patients' characteristics were similar. The hospital LOS (median, 7 days during week
39 A vs 7 days during week B, $P = 0.29$), the proportion of patients with ED-LOS <1 day (63%
40 vs 60%, $P = 0.57$) and ED antibiotic prescription (59% vs 58%, $P = 0.92$) were not
41 significantly different. Patients in the POCT arm were more frequently assigned a single
42 room when having a positive PCR for influenza, respiratory syncytial virus and
43 metapneumovirus: 52/70 (74%) vs 19/38 (50%) in the central testing arm, $P = 0.012$.

44 *Conclusions*

45 Syndromic testing performed in the ED compared to the central laboratory failed to reduce
46 the LOS or antibiotic consumption in patients with acute respiratory illness, but was
47 associated with an increased single-room assignment among patients in whom a significant
48 respiratory pathogen was detected.

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49 **Introduction**

50 Worldwide, respiratory tract infections are one of the leading causes of emergency
51 department (ED) visits ¹ and also one of the leading causes of infectious disease related
52 deaths.² Among causative pathogens of pneumonia and respiratory infections, the role of
53 viruses has recently been highlighted by the emergence of syndromic testing.³ Specifically,
54 the frequency and role of non-influenza respiratory viruses has been increasingly recognized
55 in recent years.⁴⁻¹¹ Because antibiotics overuse drives antimicrobial resistance, it is essential
56 to quickly document the agent responsible for lower-respiratory-tract infections and decide
57 whether antibiotic treatment is required. Rapid syndromic testing assays (<2 hours) have
58 been expanding in the past few years,¹² but they continue to be used primarily in central
59 laboratories despite their utility as a point-of-care test (POCT). The guidelines of the
60 Infectious Diseases Society of America recently include multiplex PCR (mPCR) as one of the
61 diagnostic tools to manage patients with lower-respiratory-tract infections who require
62 hospitalization, whether or not they are immunosuppressed.¹³

63 Several recent studies have evaluated benefits of using rapid syndromic testing assays as
64 POCTs, including decreased antibiotic use, decreased need for complementary exams
65 consumption, reduced duration of hospitalization and an increased antiviral use for influenza
66 related infections. Some of the results of these studies conflict, but two studies showed
67 substantial reductions in lengths of hospital stay and either decreases in the use of
68 antibiotics or increases in the numbers of patients receiving a single dose of antibiotics.¹⁴⁻¹⁶
69 However, a limitation of these two studies is that they often compared the use of rapid
70 syndromic testing as a POCT targeting multiple viruses and some atypical bacteria to the use
71 of a classic central laboratory approach without the use of rapid syndromic testing (i.e.
72 systematically testing for influenza but testing for other respiratory viruses only on physician
73 request). Thus, the observed benefits could be explained both by the delay of results and by
74 the systematic detection of all respiratory viruses.

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75 Isolation management is becoming an topic of great interest in the context of the COVID-19
76 pandemic and may be complexified with the potential co-circulation of SARS-CoV-2 with
77 other respiratory viruses.¹⁷ POCTs have the potential to contribute substantially in this
78 regard, because they are the only approach that facilitate a result that is timely enough to
79 inform decisions about whether patients should be assigned to a single room.¹⁸

80 We therefore designed a monocentric, quasi-randomized, prospective study to measure the
81 impact of using the same rapid syndromic test as a POCT versus in the central laboratory.
82 Measured outcomes were antibiotic consumption, hospital and ED lengths of stay and
83 assignment of patients to single rooms.

84 **Patients and Methods**

85 *Ethics*

86 The research was conducted in accordance with the Declaration of Helsinki and it was
87 approved by the local ethics committee (CEERB N2019-050).

88 *Study design and participants*

89 We performed a quasi-experimental, pragmatic, prospective monocentric study at the 850-
90 bed Bichat-Claude Bernard university hospital emergency department (ED) in Paris, France.
91 The hospital has 455 single rooms and 276 double rooms. The study design comprised
92 weekly alternate periods. During the POCT period (week A), mPCR testing was performed in
93 the ED 24 hours per day, 7 days per week. During the central laboratory period (week B),
94 mPCR testing was performed in the hospital's central virology laboratory. The laboratory was
95 able to receive samples and perform mPCR testing each weekday between 8 am and 5 pm
96 and each Saturday between 8 am and 1 pm, but not overnight or between 1 pm on Saturday
97 and Monday 8 am.

98 Patients were included during the 2019-2020 winter period, from 19 November 2019 to 9
99 March 2020. The latter date corresponds to the emergence of the COVID-19 pandemic and

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100 the French national recommendation to perform SARS-CoV-2 systematic testing among
101 patients seeking care in the ED. Before this date, no patients suspected of having COVID-19
102 were admitted to the hospital ED; instead, they were sent to a dedicated unit in the infectious
103 diseases department.

104 Included patients were adults (aged >18 years) presenting symptoms compatible with a
105 respiratory infection according to the definition of influenza-like illness (ILI) provided by the
106 European Centre for Disease Prevention and Control and requiring hospitalization.

107 Demographic and clinical data were collected at recruitment; outcome data were collected
108 retrospectively from electronic medical records. We collected all the data on a standard case
109 report form on a protected server.

110 *Procedures*

111 For respiratory viruses testing, we used the QIAstat-Dx Respiratory Panel V2 (Qiagen,
112 Hilden, Germany). This rapid multiplex PCR assay allows the detection of 22 viral and
113 bacterial respiratory targets, including: influenza (A and B); parainfluenza 1 to 4 (PIV);
114 rhinovirus/enteroviruses (HRV); respiratory syncytial viruses (RSV) A and B; human
115 metapneumovirus (hMPV); adenoviruses (ADV); human coronaviruses HKU1, OC43, NL63
116 and 229E; bocavirus; *Mycoplasma pneumoniae*; *Legionella pneumophila*; and *Bordetella*
117 *pertussis*. Results are provided within about 1 hour. During the central testing arm (A weeks),
118 the analyzer was operated by a laboratory technician in the hospital's central virology
119 laboratory. During the POCT arm (B weeks), it was operated by trained ED physicians (n=30)
120 using the swab port and analyzer located in the ED.

121 *Outcomes*

122 The primary outcome measure was the hospital length of stay (LOS). Secondary outcomes
123 were the proportion of ED lengths of stay (ED-LOS) <1 day, antibiotic prescription and
124 assignment of patients to a single room or a double room with a blocked bed, meaning that

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125 the second bed could not be used. The global disease's severity was also assessed for each
126 patient using the CRB65 score.¹⁹ The type of admission (hospital ward or intensive care unit)
127 was also retrieved. Of note, local recommendation for isolation requires that all patients with
128 a positive test for an influenza, RSV or hMPV be assigned to a single room.

129 *Statistical analysis*

130 Sample size was calculated based on the primary outcome, with an estimated difference in
131 length of stay of 2 days, 90% power and a risk α at 5%. This difference of two days was
132 chosen by taking into account the two previous studies showing an overall reduction ranging
133 from 0.8 to 1.1 days when comparing mPCR POC testing to classical virology testing in the
134 central laboratory^{14, 15} and a post hoc analysis showing a reduction of 2.8 days when
135 providing the result in less than 1.6 hours.²⁰ Thus, the number of required subjects was 518,
136 with 259 patients per arm. Baseline characteristics within each group were summarized
137 using appropriate descriptive statistics. We used linear regression for the primary outcome
138 LOS and reported mean difference with 95% confidence interval from univariate analysis and
139 for a multivariate model including sex, age and ESI triage level as covariate. Logistic
140 regression was performed for analysis of the impact of POCT on ED-LOS <1 day and single-
141 room assignment. Odds ratio (OR) and 95% confidence interval (CI) are reported using a
142 normal approximation. The *P*-values corresponded to the Wald statistic and a threshold of
143 0.05 was used for statistical significance. Statistical analysis and data management were
144 performed on R version 4.0.3.

145 **Results**

146 *Baseline characteristics*

147 A total of 525 patients were included during the study period. Among them, 48 were excluded
148 because they were discharged without hospitalization and 13 were excluded because they
149 did not meet the inclusion criteria. Of the 474 patients that were analyzed, 275 were included
150 during POCT periods (9 weeks) and 199 during central laboratory testing periods (8 weeks)

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151 (Fig.1). Patients' characteristics in both arms were similar (Table 1). The median age was 73
152 [IQR: 62-85] years, with a majority of men (56%, n=266). Between the two arms, patients had
153 no statistically significant differences in initial clinical presentation (Table 1).

154 The median turnaround time for mPCR results was 1.1 hour [IQR: 1.1-1.1] and 19.6 hours
155 [IQR: 12.7-39.2] in the POCT and central testing arms ($P < 0.001$). A total of 186 (39.2%)
156 patients had a positive PCR for a at least one respiratory pathogen, including 13 (3%) cases
157 of pathogen codetection. Identified pathogens included 55 influenza (30%, including 49
158 influenza A and 6 influenza B), 54 HRV (30%), 30 RSV (15%), 23 hMPV (12%), 19 human
159 coronaviruses (10%), 11 parainfluenza (6%), 3 *Mycoplasma pneumonia* (2%), 1 *Legionella*
160 *pneumophila* (1%) and 1 bocavirus (1%). No statistically significant differences were
161 observed between the arms in the pathogens' distribution (Table 3).

162 *Primary outcomes*

163 For the primary outcome, hospital LOS, we did not observe any difference between the
164 POCT and the central testing arms. The mean difference adjusted for sex and age was 0.3
165 (95%CI, -1.2-2.8; $P = 0.66$).The median LOS stay was 7 days (IQR: 3-14) in the POCT arm
166 and 7 days (IQR: 2-13) in the central testing arm. The multivariate analysis showed that the
167 severity, as assessed by CRB65 score, was associated with a longer length of stay (OR 1.2
168 for one each point; 95% CI, 1.1-2.4; $P = 0.04$) (Table 2).

169 In the univariate analysis, the proportions of patients with ED-LOS <1 day were not
170 significantly different between the two arms (OR 1.1; 95% CI, 0.8-1.6) (Table 3). No
171 statistically significant differences were observed between the POCT testing arm and the
172 central testing arm regarding the duration of antibiotic treatment. We observed no statistically
173 significant difference regarding antibiotic prescription or ward of admission between the two
174 arms (Table 1). The median durations of treatment were similar in both arms: two days for 3rd
175 generation cephalosporin ($P = 0.14$), two days for macrolides ($P = 0.43$) and five days for
176 amoxicillin ($P = 0.77$).

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177 Patients in the POCT arm were more frequently assigned to a single room after admission
178 when having a positive PCR for influenza, RSV and metapneumovirus pathogens (52/70
179 (74%) in the POCT arm versus 19/38 (50%) in the central testing arm, $P = 0.019$, OR, 2.9;
180 95% CI, 1.3–6.7; $P = 0.012$). Multivariate analysis confirmed these associations between
181 POCT testing and single-room assignment (OR, 2.9; 95% CI, 1.3–6.8; $P = 0.014$) (Table 4).
182 No statistical differences were observed for patients admitted into single rooms with either a
183 negative PCR or a positive PCR for any other virus between the POCT and central testing
184 arm (66/161 patients (34%) in the POCT arm versus 70/205 patients (40%) in the central
185 testing arm, $P = 0.36$) (Table 5).

186 Discussion

187 This large, pragmatic, quasi-randomized prospective controlled trial compared the impact of
188 a uniform mPCR respiratory pathogen testing approach performed as a POCT in the ED to
189 testing performed in a central virology laboratory. The median delay to result decreased from
190 19.6 hours in the central laboratory to 1.1 hours in the POCT arm. POCT mPCR did not
191 shorten hospital LOS nor reduce prescription of antibiotic treatment. However, a higher rate
192 of compliance with local isolation recommendations in terms of assigning patients to single
193 rooms was observed. Thus, POCT increased the proportion of patients isolated due to a
194 positive PCR for influenza, RSV, or metapneumovirus, from 50% in the central laboratory
195 arm to 74% in the POCT arm ($P = 0.019$).

196 Our results regarding LOS and antibiotic use seem inconsistent with the findings of two
197 previous studies^{14, 15} that were assessing the benefits of both quicker results and wider
198 pathogen detection. We expected a decrease in antibiotic use in the POCT arm due to the
199 rapid diagnosis of viral respiratory infection. However, a viral infection does not exclude a
200 bacterial coinfection^{7, 21} and viro-bacterial coinfections may even be associated with more
201 severe prognoses.^{8, 9}

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202 To our knowledge, very few studies have assessed the impact of rapid molecular testing on
203 isolation for respiratory viruses.^{14, 22} However our study showed a positive impact on
204 compliance with preventive measures by increasing single-room assignment in the
205 downstream unit among patients with a viral infection that requires isolation. These
206 measures are critical for reducing nosocomial transmissions and outbreaks. This is
207 particularly relevant because nosocomial acquisition of influenza is associated with more
208 severe cases and substantially increases hospital LOS.^{23, 24} The same impact could also be
209 expected for other viruses, but very few data are available aside from data related to
210 influenza.^{9, 10}

211 The emergence of SARS-CoV-2 has highlighted the need for more efficient respiratory
212 control measures. In this context, our results are in line with a study¹⁸ that demonstrated that
213 rapid POCT for SARS-CoV-2 decreased the time to availability of results compared with
214 laboratory PCR (1.7 versus 21.3 hours); this reduction was associated with improved
215 infection control measures and reduced patient time in the ED before hospitalization. It is
216 likely that SARS-CoV-2 will continue to circulate and burden health systems for years to
217 come. Thus, forthcoming testing strategies will be impacted by the potential co-circulation of
218 SARS-CoV-2 with the other major respiratory pathogens, such as influenza, coupled with
219 uncertainty about the duration of protection after infection or potential vaccination. In those
220 strategies, it will be critical to be able to accurately detect pathogens of concern and
221 appropriately isolate patients.

222 Our study has several limitations. Firstly, it is a monocentre study conducted in a center with
223 prior experience in systematic mPCR testing. During the previous winter, POCT had already
224 been introduced for a more restricted population,²⁵ so the ED physicians were already trained
225 in clinical use of those results. Our findings should be replicated in further studies in other
226 centres, because some results may be dependent on the specific health care system and
227 local setting. Secondly, due to the study's objective, it was not possible to blind physicians
228 from a POCT or central laboratory randomization group. Thirdly, the use of randomized

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229 weekly periods may not be ideal, as the epidemiological situation can change from one week
230 to another. However, we did not observe significantly different distributions of patients or
231 pathogens between the two time periods. Additionally, individual randomization would have
232 blurred the potential effects of ED length duration and room assignments. Only half of the
233 patients each day would have benefited from the shorter time to results. The other half would
234 have been placed blindly, thus potentially depriving some patients of a more appropriate
235 room assignment.

236 In conclusion, the use of mPCR POCTs for adults with acute respiratory illness seeking care
237 in the ED failed to reduce the LOS or antibiotic consumption. On the other hand, the mPCR
238 POCT approach was associated with an increased single-room assignment among patients
239 positive for a significant respiratory pathogen. Routine mPCR POCT for respiratory viruses
240 should be more widely introduced into diagnostic pathways for adults presenting to hospitals
241 with acute respiratory infections to improve compliance with preventive measures and reduce
242 nosocomial outbreaks.

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243

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344

345 **Table 1.** Comparison of patients' baseline characteristics and prognosis.

Variables	All (n = 474)	Point-of-care testing (n = 275)	Central testing (n = 199)	P value*
Patient characteristics				
Male, n (%)	266 (56)	154 (56)	112 (56)	1
Age (years), median (IQR)	73 (62-85)	73 (62-84)	72 (60-85)	0.41
Temperature (°C), median (IQR)	37 (37-38)	37 (37-38)	37 (36-38)	0.48
Systolic blood pressure (mmHg), median (IQR)	131 (113- 149)	131 (114-151)	129 (112-145)	0.11
SpO2 (%), median (IQR)	95 (92-97)	95 (91-97)	95 (93-98)	0.51
Heart rate (bpm), median (IQR)	94 (81-110)	95 (81-110)	92 (82-107)	0.18
Respiratory rate (min), median (IQR)	19 (16-24)	20 (17-25)	18 (16-22)	0.09
Duration of symptoms before ED visit (days), median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	0.65
CRB-65 score, median (IQR)	1 (1-1)	1 (1-2)	1 (1-1)	0.14
Charlson Score, median (IQR)	4 (3-6)	5 (3-6)	4 (3-6)	0.12
PCR turnaround times (hours), median (IQR)		1.1 (1.1-1.1)	19.6 (12.7-39.2)	
Virological results				
Negative PCR, n (%)	288 (61)	155 (56)	133 (67)	0.02
Positive PCR, n (%)	186 (39)	120 (44)	66 (33)	0.02
Coinfections, n (%)	13 (3)	7 (3)	6 (3)	0.78
Identified pathogens, n (%)				0.25
Influenza A	49 (25)	35 (28)	14 (20)	
Influenza B	6 (3)	4 (3)	2 (3)	
Enterorhinovirus	54 (27)	32 (25)	22 (31)	
Metapneumovirus	23 (12)	16 (13)	7 (10)	
RSV	30 (15)	15 (12)	15 (21)	

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Parainfluenza	11 (6)	8 (6)	3 (4)	
Coronavirus	19 (10)	15 (12)	4 (6)	
<i>M. pneumoniae</i>	3 (2)	1 (1)	2 (3)	
<i>L. pneumophila</i>	1 (1)	0 (0)	1 (1)	
Bocavirus	1 (1)	1 (1)	0 (0)	
Patient management, n (%)				
Isolation (<i>n</i> = 473)				
Single room	195 (41)	116 (42)	79 (40)	0.69
Double room with blocked bed	272 (57)	156 (57)	116 (58)	
Orientation				
Medical ward	206 (43)	117 (43)	89 (45)	0.39
ICU	29 (6)	18 (7)	11 (6)	
Transfer to another hospital	171 (36)	103 (38)	68 (35)	
ED ward	118 (25)	63 (23)	55 (28)	
Antibiotics before ED visit (<i>n</i> = 471)	62 (13)	38 (14)	24 (12)	0.81
Antibiotics at the ED (<i>n</i> = 472)	275 (58)	160 (59)	115 (58)	0.92
Oseltamivir	44 (9)	30 (11)	14 (7)	0.15
Patient outcomes, n (%) (<i>n</i> = 455)				
LOS** (days)	7 (3-14)	7 (3-14)	7 (2-13)	0.29
ED-LOS < 1day	291 (61)	172 (63)	119 (60)	0.57
Patients still hospitalized at day 30	41 (9)	26 (9)	15 (8)	0.51
Patient death during hospitalization	37 (8)	25 (9)	12 (6)	0.3

346 Reported statistic: *n* (%) or med (Q1-Q3)

347 * *P* value of the Fisher or Wilcoxon test

348 ** 19 patients are missing due to an unknown length of stay; the length of stay for patients
349 still hospitalized on D30 was set at 30 days.

350 ED, emergency department; LOS, length of stay; RSV, respiratory syncytial virus

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352 **Table 2.** Factors associated with length of stay (univariate and multivariate linear regression)

Variables	Univariate analysis			Multivariate analysis (n = 440)	
	Median (Q1-Q3)	Estimation (95% CI)	P value*	Estimation (95%CI)	P value**
Study arm	Central testing	7 (2-13)	0 (ref)	0.34	0 (ref)
	POCT	7 (3-14)	0.8 (-0.9;2.6)		0.3 (-1.2;1.8) 0.66
Sex	M	7 (2-13)	0 (ref)	0.59	0 (ref)
	F	8 (3-15)	0.5 (-1.2;2.2)		0.9 (-0.6;2.4) 0.24
Age (/10 years)			0.7 (0.2;1.2)	0.003	0.3 (-0.2;0.9) 0.23
Symptom duration before ED visit (days)			0.1 (-0.1;0.3)	0.22	
CRB65 score			2.6 (1.5;3.7)	<0.001	1.2 (0.1;2.4) 0.041
Charlson's score			0.5 (0.2;0.9)	0.005	
Antibiotics before ED		8 (2-18)	1.6 (-0.9;4.1)	0.21	
Administered antibiotics in ED		7 (3-14)	0.9 (-0.8;2.6)	0.31	
Oseltamivir		6 (1-13)	-0.2 (-3.1;2.7)	0.88	
Medical ward		9 (5-15)	0 (ref)	<0.001	0 (ref)
ICU		25 (11-30)	9 (6;12.1)		8.9 (5.8;-12.1) <0.001
Transfer		9 (6-15)	0.9 (-1.0;2.8)		0.4 (-1.6;2.3) 0.72
ED ward		1 (1-2)	-8.3 (-10.1 ; -6.5)		-8 (-9.8;-6.1) <0.001
Isolation	Single room	8 (4-15)	0 (ref)	0.39	
	Double room with blocked bed	6 (2-13)	-1.2 (-2.9;0.5)		
	Double room	10 (8-10)	0.3 (-7.2;7.7)		

353 * P value of the LRT test

354 ** P value of the Wald test

355 ED, emergency department; POCT, point-of-care testing

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357 **Table 3.** Factors associated with ED length of stay (univariate logistic regression)

Variables		Univariate analysis	
		OR (95%CI)	P value
Study arm	Central testing	1 (ref)	0.54
	POCT	1.1 (0.8;1.6)	
Sex	M	1 (ref)	0.89
	F	1.0 (0.7;1.4)	
Age (years)		1.0 (1.0;1.0)	0.92
Symptom duration before			
ED visit (days)		1.1 (0.9;1.4)	0.44
CRB65 score		1.0 (0.9;1.1)	0.76
Charlson's score		1.3 (0.7;2.3)	0.4
Antibiotics before ED		1.0 (0.7;1.4)	0.92
Oseltamivir		1.4 (0.7;2.8)	0.3
Isolation	Single room	1 (ref)	0.3
	Double room with a blocked bed	0.8 (0.5;1.1)	
	Double room	1.3 (0.3;9.6)	

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359 ED, emergency department; POCT, point-of-care testing

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360

361 **Table 4.** Factors associated with the prescription of suitable single room assignment
 362 (univariate and multivariate logistic regression)

Variables	Univariate analysis (<i>n</i> = 108)		Multivariate analysis	
	OR (95%CI)	<i>P</i> value*	OR (95% CI)	<i>P</i> value**
Study arm	Central testing	1 (ref)	0.012	1 (ref)
	POCT	2.9 (1.3;6.7)		2.9 (1.3;6.8) 0.014
Sex	M	1 (ref)	0.62	1 (ref)
	F	0.8 (0.4;1.8)		0.9 (0.4;2.2) 0.86
Age (years)		1.0 (1.0;1.0)	0.95	1.0 (1.0;1.0) 0.79
Symptoms duration before ED visit (days)		1.0 (0.9;1.2)	0.89	
CRB65 score		1.0 (0.6;1.8)	1	
Charlson's score		1.0 (0.8;1.2)	0.89	
Antibiotics before ED		0.9 (0.3;2.5)	0.84	
ED antibiotics administration		0.6 (0.2;1.3)	0.18	
Oseltamivir		1.0 (0.4;2.3)	0.93	

363 * *P* value of the LRT test.364 ** *P* value of the Wald test.

365 ED, emergency department; POCT, point-of-care-testing

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367 **Table 5.** Multiplex PCR result and single room assignment of patients isolated by pathogen

	Single room assignment, central testing period, <i>n/N</i> (%)	Single room assignment, POCT period, <i>n/N</i> (%)	<i>P</i> value*
Overall single room assignment	82/199 (41)	119/275 (43)	0.72
Pathogen with local recommendation for single room assignment*	19/38 (50)	52/70 (74)	0.019
Influenza A	8/14 (57)	27/35 (77)	0.18
Influenza B	1/2 (50)	4/4 (100)	0.33
Metapneumovirus	1/7 (14)	11/16 (69)	0.027
RSV	9/15 (60)	10/15 (67)	1
Unrequired single room assignment	66/161 (40)	70/205 (34)	0.36
Rhinovirus	8/19 (42)	7/28 (25)	0.34
Parainfluenza	2/3 (67)	2/8 (25)	0.49
Coronavirus	2/3 (67)	8/13 (62)	1
Negative PCR	53/133 (40)	53/155 (34)	0.33

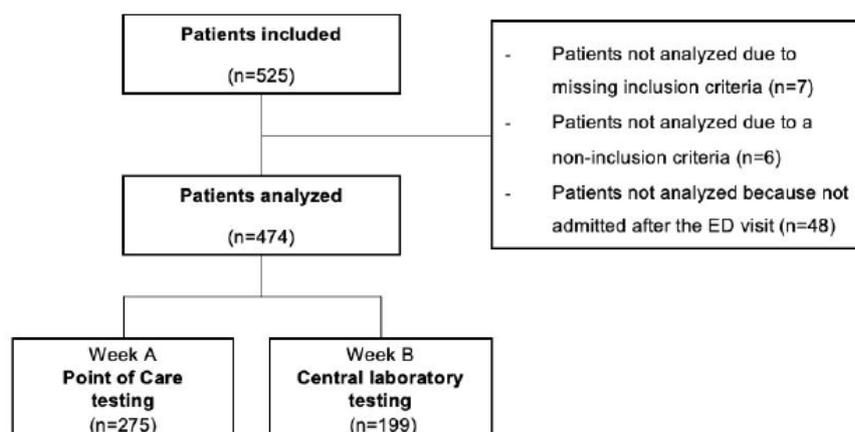
368 Reported statistic: *n* (%)369 * *P* value of the Fisher test

370 POCT, point-of-care testing; RSV, respiratory syncytial virus

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372 **Figure 1.** Study flow chart



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374 ED, emergency department

Caractéristiques associées à la COVID-19 ou autres infections virales respiratoires : étude monocentrique dans un service d'accueil des urgences.

Contexte et objectif

Les premiers cas de maladie à coronavirus 2019 (COVID-19) ont été signalés en décembre 2019, à Wuhan, en Chine [1]. Après une propagation rapide dans le monde, la maladie a été déclarée comme pandémie en mars 2020. Au 9 mars 2021, plus de 117 millions de cas confirmés de COVID-19, y compris 2,6 millions de décès ont été recensés à travers le monde [43].

Le virus est donc susceptible de continuer à circuler et en étant associé à une forte morbi-mortalité pendant une période prolongée. Dans un tel scénario, le virus SARS-CoV-2 co-circulera probablement avec d'autres virus respiratoires (VR) notamment pendant l'hiver dans l'hémisphère nord [77]. Une telle co-circulation a été brièvement observée en Amérique du Nord et en Europe au début des flambées locales de SRAS-CoV-2 [78]. Dans cette situation, tout malade se présentant avec un syndrome grippal (ILI) pourrait être infecté par n'importe quel virus respiratoire, y compris le SARS-CoV-2, ce qui soulève un défi supplémentaire pour le diagnostic et l'isolement des patients dans un service d'accueil des urgences.

Nous avons profité de l'étude prospective en cours dans notre service d'urgence, évaluant l'impact des tests au point de service avec une PCR multiplex, pour en utiliser l'infrastructure et recueillir les caractéristiques cliniques des patients se présentant. Nous avons ensuite analysé les caractéristiques qui aident à différencier la COVID-19 des autres infections virales respiratoires.

Méthodes

Il s'agit d'une étude de cohorte prospective composée de patients consécutifs consultant pour un syndrome grippal. Deux périodes temporelles ont été définies, la première s'étendant de décembre 2019 à février 2020 et représentant la période où seuls les autres virus respiratoires circulaient et la seconde celle du mois de mars 2020 représentant la période SARS-CoV-2 .

Les données démographiques et cliniques ont été collectées de manière prospective pendant les deux périodes, y compris l'âge, le sexe, les symptômes respiratoires, le temps écoulé depuis l'apparition des symptômes, les comorbidités et les paramètres cliniques à l'admission aux

urgences. Les données biologiques ont également été enregistrées : numération formule sanguine, CRP et NT-pro -BNP.

Stratégie de modélisation pour évaluer l'effet de la co-circulation de SARS-CoV-2 et autres virus respiratoires

Sous l'hypothèse d'une co-circulation du SARS-CoV-2 et d'autres VR, nous avons modélisé les chances d'avoir une PCR positive pour le SARS-CoV-2 par rapport à d'autres virus. Nous avons eu recours à la méthode bayésienne pour cette partie.

Analyses statistiques

Les caractéristiques de base de chaque groupe ont été décrites avec des nombres et des pourcentages pour les variables qualitatives et par la médiane et l'intervalle interquartile (IQR) pour les variables quantitatives. Nous avons évalué les facteurs associés à une PCR positive pour le SARS-CoV-2 pendant la période du SARS-CoV-2 et pour d'autres VR pendant la période des VR en utilisant une régression logistique univariée. Nous avons ensuite utilisé un modèle multivarié parmi les variables avec une valeur p inférieure à 0,05 dans l'analyse univariée et une proportion de valeurs manquantes inférieure à 20%.

Résultats

Respectivement 508 et 596 patients ont été inclus durant les deux périodes. Les patients étaient plus fréquemment des hommes, respectivement 57% (289/508) et 59% (354/596). L'âge médian était respectivement de 73 [63–85] ans et 60 [46–76] ans ($p < 0,001$).

Résultats virologiques

Au cours de la période VR, 216/508 (43%) patients avaient une mPCR positive, dont 13 doubles co-infections virales, avec la distribution virale suivante: 68 (31%) rhinovirus, 60 (28%) influenza, 35 (16%) VRS, 30 (14%) métapneumovirus humain, 28 (13%) coronavirus, quatre (2%) parainfluenza, trois (0,1%) adénovirus et un (0,5%) bocavirus.

Au cours de la période SARS-COV-2-CoV2, 268/596 (45%) patients ont eu une PCR positive pour le SARS-CoV-2, et 70 autres infections virales respiratoires ont également été identifiées, dont 18 co-infections avec le SARS-CoV-2.

Les caractéristiques des patients associées à la détection d'un virus respiratoire non SARS-CoV-2

La durée médiane des symptômes était de 2 [1–4] jours avant l'arrivée aux urgences. Les caractéristiques suivantes ont été associées à une mPCR positive dans l'analyse univariée : le jeune âge, la présence de fièvre, de toux et les expectorations, et la diminution du nombre de globules blancs et de plaquettes. Ces variables ont également été récupérées dans l'analyse multivariée (Tableau 6).

Les caractéristiques cliniques et biologiques associées à la détection du SARS-CoV-2

La durée médiane des symptômes était de 3 [2–7] jours et les caractéristiques suivantes étaient associées à une PCR SARS-COV-2 positive : le sexe masculin, le jeune âge, la fièvre, les frissons, les myalgies, la toux, les crépitations bilatéraux, le diabète, l'absence de pathologie respiratoire chronique, les antécédents d'accident vasculaire cérébral, la fréquence respiratoire plus élevée, l'élévation de la CRP, la diminution du NT-proBNP, la diminution du nombre de leucocytes et de lymphocytes et la diminution du nombre de plaquettes. Dans l'analyse multivariée, les caractéristiques suivantes sont restées associées à la détection du SARS-CoV-2 : le jeune âge, le sexe masculin, la fièvre, les frissons, les myalgies, la fréquence respiratoire plus élevée et l'absence de maladie pulmonaire chronique (Tableau 6). Une PCR positive pour le SARS-CoV-2 était également associée à l'admission aux soins intensifs (OR, 8,4 ; IC à 95%, 4,6–16,8; $p < 0,001$) et à la mortalité pendant l'hospitalisation (OR, 3,0; IC à 95%, 1,8–5,2; $p < 0,001$) .

Comparaison des caractéristiques associées à un VR ou au SARS-CoV-2

Sous l'hypothèse de la co-circulation du SARS-CoV-2 avec des VR, les variables associées au diagnostic virologique SARS-CoV-2 vs VR) parmi les mPCR positives étaient le sexe masculin, l'absence de maladie pulmonaire chronique, l'âge, la présence de fièvre et l'absence d'expectoration. Un score clinique basé sur cette analyse multivariée a été calculé en utilisant des coefficients entiers basés sur des logarithmes OR, allant de -6 à +5 (Tableau 7). A noter, avec un score supérieur ou égal à 1, la sensibilité et la spécificité étaient respectivement de 91% et 52%.

	PCR + au cours de la période RV (N=492)*		PCR + au cours de la période SARS-CoV-2 (N=582)*		SARS-CoV-2 vs les autres VR (overall study period)**	
	ORa (95% CI)	p	ORa(95% CI)	p	ORa(95% CI)	p
Age	0.89 (0.80-1.00)	0.041			0.80 (0.72-0.89)	<0.001
Sexe masculin			2.23 (1.53-3.25)	<0.001	1.64 (1.10-2.44)	0.015
Expectoration	1.70 (1.05-2.75)	0.031			0.13 (0.07-0.26)	<0.001
Fièvre	1.60 (1.08-2.38)	0.02	3.33 (2.25-4.97)	<0.001	3.27 (2.17-4.94)	<0.001
Frissons			1.62 (1.03-2.56)	0.038		
Myalgies			1.72 (1.10-2.70)	0.017		
Toux	2.16 (1.43-3.30)	<0.001				
Diabète						
IRC			0.40 (0.24-0.64)	<0.001	0.40 (0.25-0.64)	<0.001
FR (min ⁻¹)			1.06 (1.02-1.09)	<0.001		
Plaquettes (per 100G/L)	0.69 (0.54-0.85)	<0.001				
Leucocytes (per G/L)	0.97 (0.93-1.01)	0.11				

* Nombre de patients inclus dans cette analyse, à l'exclusion des patients avec des valeurs manquantes

** soit 40 et 45% pour les virus non SARS-COV-2 et SARS-COV-2, respectivement

IRC : insuffisance respiratoire chronique

FR : fréquence respiratoire

Tableau 6. Analyse multivariée de la PCR positive pour les deux périodes (virus respiratoires non SARS-CoV-2 (RV) et SARS-CoV-2) séparément, et pour SARS-CoV-2 vs RV dans une période de co-circulation modélisée.

Variable	score
Fièvre	2
Age < 60	2
Sexe masculin	1
IRC	-2
Expectoration	-4

Tableau 7. Le score clinique pour la suspicion de SARS-COV-2 et d'autres virus respiratoires. Un score strictement supérieur à un a une sensibilité de 83% et une spécificité de 65% de présenter un SARS-CoV-2 au lieu de tout autre virus respiratoire en cas de PCR positive.

Discussion

Dans cette large cohorte prospective monocentrique, incluant respectivement 508 et 596 patients consécutifs atteints de syndrome grippal consultant aux urgences pendant les périodes VR et SARS-CoV-2, nous avons identifié plusieurs caractéristiques cliniques associées à une PCR virale positive.

La capacité de distinguer la COVID-19 des autres infections virales respiratoires pourrait devenir un problème si la circulation du SARS-CoV-2 se poursuit. Si l'épidémie grippale a été presque inexistante sur la période hivernale 2020-21, au moment de l'écriture de cette thèse [79,80], certains virus comme le VRS ou le rhinovirus continuent à circuler et on peut supposer que la plupart des autres virus respiratoires réapparaîtront au relâchement des mesures barrières alors que le SARS-CoV-2 n'aura toujours pas disparu.

Les caractéristiques observées dans notre cohorte pour les patients COVID-19 sont en accord avec les rapports précédents [81]. La plupart de ces caractéristiques cliniques sont également associées à d'autres infections virales respiratoires observées dans notre étude et dans d'autres travaux antérieurs [82,83]. En analysant la force des associations de ces caractéristiques cliniques avec la positivité de la PCR au SARS-CoV-2 ou aux VR, nous avons pu définir un ensemble limité de marqueurs cliniques associés à un risque plus élevé d'être infecté par le SARS-CoV-2: être de sexe masculin, d'un plus jeune âge, avec de la fièvre et en l'absence d'expectoration est prédictif d'une infection par le SARS-CoV-2 tandis que le fait d'avoir des maladies pulmonaires chroniques est un prédicteur d'un virus respiratoire non SARS-CoV-2. Notre étude présente plusieurs limites. Premièrement, il s'agit d'une étude monocentrique, et la période des autres virus respiratoires a été conçue avant l'émergence du SARS-CoV-2, donc certains marqueurs n'ont pas pu être recueillis. Enfin, les caractéristiques identifiées pourraient évoluer dans les années à venir avec la vaccination en cours de la population générale.

En conclusion, les symptômes associés au SARS-CoV-2 et à d'autres infections virales respiratoires sont fréquemment partagés (8). Cela pose des défis potentiels dans la prise en charge des patients en cas de co-circulation importante de tous ces virus. Le score que nous avons proposé, reste à valider, et ne peut uniquement être utile pour faire du tri à l'arrivée aux urgences et ne remplace en aucun cas la confirmation virologique, d'ailleurs les efforts principaux se concentrent sur l'élaboration de tests de diagnostic moléculaire rapides, faciles d'usage, délocalisés et disponibles en quantité.

Au total, ce travail nous a permis de déterminer un certain nombre de facteurs plus associés à l'infection par le SARS-CoV-2 que par d'autres virus respiratoires : le sexe masculin, la fièvre, l'âge plus jeune, l'absence de pathologie pulmonaire chronique et d'expectoration. Ces facteurs évoluent avec la progression continue de la pandémie. La seule certitude diagnostique n'est cependant permise que par la PCR et des efforts considérables ont été réalisés sur les délais de rendu de résultat et la délocalisation des techniques.

RESEARCH ARTICLE

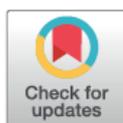
Characteristics associated with COVID-19 or other respiratory viruses' infections at a single-center emergency department

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Data Availability Statement: Regarding data sharing, we are not allowed to share the data publicly as, according to French ethical laws, the raw data of epidemiological study collected as part of the medical follow-up on the framework of standard medical care cannot be shared, even anonymously, without a specific ethical committee approval. However these data are secured in our laboratory system, as required by the ISO15189 certification of our laboratory, and can be shared on request approved by an adequate ethical

Abstract

Background

Rapid identification of patients with high suspicion of COVID-19 will become a challenge with the co-circulation of multiple respiratory viruses (RVs). We have identified clinical or biological characteristics to help distinguish SARS-CoV-2 from other RVs.

Methods

We used a prospective cohort including all consecutive patients admitted through the emergency department's (ED) and presenting respiratory symptoms from November 2019 to April 2020. Patients were tested for RV using multiplex polymerase chain reaction (mPCR) and SARS-CoV-2 RT-PCR.

Results

203/508 patients were positive for an RV during the non-SARS-CoV-2 epidemic period (November to February), and 268/596 patients were SARS-CoV-2 positive during the SARS-CoV-2 epidemic (March to April). Younger age, male gender, fever, absence of expectoration and absence of chronic lung disease were statistically associated with SARS-CoV-2 detection. Combining these variables allowed for the distinguishing of SARS-CoV-2 infections with 83, 65, 75 and 76% sensitivity, specificity, PPV and NPV, respectively.

Conclusion

Patients' characteristics associated with a positive PCR are common between SARS-CoV-2 and other RVs, but a simple discrimination of strong SARS-CoV-2 suspicion with a limited

committee. Interested researchers may submit queries related to data access to the catherine.gillet3@aphp.fr.

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set of clinical features seems possible. Such scoring could be useful but has to be prospectively evaluated and will not eliminate the need for rapid PCR assays.

Introduction

The first cases of coronavirus disease 2019 (COVID-19) were reported in December 2019, in Wuhan, China [1]. After a rapid spread worldwide, the disease was declared a pandemic in March 2020. As of August 10, 2020, over 19 million confirmed cases of COVID-19, including 728,013 deaths [2]. In France, the first case of COVID-19 was identified in Bichat Claude Bernard university hospital, in Paris, on January 24, 2020, concomitant with the end of the annual influenza epidemic [3]. As in most countries struck by the virus, the pandemic's first wave was controlled in France due to a national lockdown that began on March 16, 2020. However, new waves are striking again in several countries with initially controlled outbreaks, and the pandemic is still accelerating worldwide [4].

The virus is thus highly likely to continue to circulate for a prolonged period. In such a scenario, the SARS-CoV-2 virus will likely co-circulate with other respiratory viruses (RVs) during the next fall and winter in the northern hemisphere or during the ongoing months in the southern hemisphere [5]. Such co-circulation was briefly observed in Northern America and Europe at the beginning of the SARS-CoV-2 local outbreaks [6, 7]. As patients presenting with influenza-like illnesses (ILIs) could be infected by any RV, including SARS-CoV-2, this will raise an additional challenge for patients' diagnosis and isolation in an emergency department (ED). The looming threat of concurrent SARS-CoV-2 and other RV epidemics is an increasing concern for both physicians and health policies [8]. Being able to quickly identify and isolate patients who are highly suspected of having COVID-19 is indeed a cornerstone of preventing nosocomial transmission of this new and deadly infection in crowded EDs and other units.

We took advantage of an ongoing prospective study assessing the impact of point-of-care testing with multiplex PCR in our ED to extend the study. We aimed to identify clinical and biological characteristics that help to differentiate COVID-19 from other respiratory viral infections.

Methods

Patients and inclusion criteria

Bichat-Claude Bernard hospital is a large 850-bed university reference center for high-risk pathogens in Northern Paris. All consecutive patients presenting with an ILI and admitted to the hospital through the ED were prospectively included from November 18, 2019, to March 30, 2020. All were tested for respiratory viral infection using mPCR assay (see below). Our ED's first COVID-19 case was identified on February 28, and systematic on-site specific SARS-CoV-2 RT-PCR began on March 2, 2020.

An ILI was defined as the association of at least one systemic symptom (fever with a temperature higher than 38.5°, malaise, headache, and myalgia) with one respiratory symptom (cough, sore throat, and dyspnea), according to the eCDC ILI definition [9]. Those indications of PCR testing were identical during both periods in our ED despite the constraints of the epidemics.

Study periods

In France, the influenza epidemic period extended from November 18, 2019, to March 2, 2020. During this period, SARS-CoV-2 was not spreading in the community or among

patients returning or traveling from foreign countries, notably Northern Italy and China. All suspicions of SARS-CoV-2 based on these exposures were thus admitted from other EDs or hospitals in the dedicated ward of the Infectious Diseases department and were not included in this study. Starting on March 3, all patients with an ILI visiting the ED were systematically suspected of COVID-19 and tested for both human RVs and SARS-CoV-2.

To reflect these two periods, they were analyzed separately: (i) Period 1, hereafter called the respiratory virus (RV) period, with an active circulation of non-SARS-CoV-2 RVs, from November 18, 2019 to March 2, 2020, and (ii) Period 2, hereafter called the SARS-CoV-2 period with active circulation of SARS-CoV-2, starting on March 3.

Virological testing

During the RV period, multiplex PCR was performed as point of care using the QIAstat-Dx Respiratory Panel (QIAGEN, Hilden, Germany). This rapid multiplex PCR assay allows for detecting 22 viral and bacterial respiratory targets, including influenza, parainfluenza, rhinoviruses/enteroviruses, RSV, metapneumovirus, adenovirus, coronaviruses, bocavirus, *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Bordetella pertussis* [10]. During the SARS-CoV-2 period, and depending on kit availability, viral investigations were conducted either with the QIAstat-Dx Respiratory SARS-CoV-2 Panel (Qiagen, Hilden, Germany), allowing for the detection of the same respiratory pathogens plus SARS-CoV-2 [11], or with a combination of the RT-PCR RealStar SARS-CoV-2 Kit RUO (Altona Diagnostics, Hamburg, Germany) [12] and rapid multiplex PCR FilmArray RP2 (BioFire, BioMérieux, Marcy-L'Etoile, France) [13], allowing for the detection of the same viral respiratory pathogens except bocavirus.

Clinical and biological data

Demographic and clinical data were prospectively collected, including age, sex, respiratory symptoms (e.g., cough, dyspnea, expectoration, chest pain, and auscultatory abnormalities), time since the onset of symptoms, comorbidities (e.g., diabetes, history of stroke, myocardial infarction, chronic heart failure, chronic kidney failure, chronic bronchitis, and asthma) and clinical parameters at ED admission (e.g., temperature, blood pressure, cardiac frequency, respiratory frequency, oxygen saturation, and Glasgow coma score). The following biological data were also recorded: blood counts, C-Reactive Protein, and NT-pro brain natriuretic peptide (NT pro-BNP). Based on the ongoing acquisition of COVID-19-related symptoms, diarrhea, anosmia, and ageusia were added to data recording after the beginning of the SARS-CoV-2 period.

Modeling strategy for assessing the effect of the co-circulation of SARS-CoV-2 and other respiratory viruses

Under the hypothesis of a co-circulation of SARS-CoV-2 and other RVs, we modelled the odds of having a positive PCR for SARS-CoV-2 with respect to other viruses, given that the PCR is positive. For the sake of clarity, we denoted the sample by S , with the convention $S = 1$ for the SARS-CoV-2 period and $S = 2$ for the RV period. We considered a mixture of SARS-CoV-2 and RV period with parameter $p = P(S = 1)$. According to Bayes formula, the probability of a random observation from the mixture actually being drawn from Sample 1 given that the PCR is positive is as follows:

$$P(S = 1 | PCR+) = \frac{P(PCR+ | S = 1)p}{P(PCR+ | S = 1)p + P(PCR+ | S = 2)(1 - p)}$$

and the corresponding odds are

$$O(S = 1|PCR+) = \frac{P(PCR+ | S = 1)p}{P(PCR+ | S = 2)(1 - p)}$$

Therefore, if we consider a binary covariate X , the odds ratio for being COVID+ in the strata $X = 1$ with respect to the strata $X = 0$ can be written as follows:

$$OR_{s,X|PCR+} = \frac{RR_{PCR,X|1}}{RR_{PCR,X|2}} OR_{s,X} \quad (1)$$

where $RR_{PCR,X|s}$ denotes the relative risk of having a positive PCR in the strata $X = 1$ with respect to $X = 0$, given that the observation belongs to sample s . This equality, initially derived in the case of a binary covariate X , can be straight forwardly extended to the case of categorical or quantitative variables and covariate-adjusted quantities.

Eq (1) has a clear interpretation in the sense that it identifies two independent contributions to the quantity $OR_{s,X|PCR+}$. The first one is the ratio between two relative risks and reflects the difference of association between the covariate and the PCR diagnosis in both samples. If, for example, the male sex is strongly associated with a higher risk of having a positive PCR for SARS-CoV-2, but no association exists for other RVs, then a positive PCR drawn from the mixture sample tends to more likely be for SARS-CoV-2 if the patient is male. The second contribution comes from the imbalance between both samples for covariate X . If, for example, patients from the SARS-CoV-2 period are significantly younger, then a positive PCR in a young patient is more likely to be a COVID case.

Statistical analysis

The baseline characteristics within each group were described with numbers and percentages for qualitative variables and median and interquartile range (IQR) for quantitative variables.

We assessed factors associated with a positive PCR for SARS-CoV-2 in the SARS-CoV-2 period and for other RVs in the RV period using univariate logistic regression. For each sample and variable, we reported the Odds ratio (OR), the 95% confidence interval using a normal approximation and the p-value corresponding to the Wald statistic. We used a threshold of 0.05 for statistical significance. We then performed a multivariate model resulting from a stepwise selection procedure among variables with a p-value below 0.05 in the univariate analysis and a proportion of missing values below 20%.

Regarding the modelling of the SARS-CoV-2 risk in a co-circulation period with other RVs, we estimated relative risks on the right-hand side of Eq (1) with a quasi-Poisson regression model to take over-dispersion into account. Since these relative risks vary according to the proportion of positive PCR in both samples, we built different scenarios corresponding to different degrees of prevalence of positive PCR for SARS-CoV-2 and other RVs. Relative risks for these scenarios were estimated with a-priori weights on the observations. The quantity $[[OR]]_{(S,X)}$ and its standard error were estimated with a logistic regression from both samples' union. Finally, the estimate for $[[OR]]_{(S,X|PCR+)}$ was reported, and its 95% confidence interval was derived with a normal approximation under the hypothesis of independence between its components.

We also performed a multivariate model for the quantity $[[OR]]_{(S,X|PCR+)}$ by using multivariate models for the right-hand side of (1) and a stepwise selection procedure based on covariates with $p < 0.05$ in the univariate analysis and less than 20% of missing data. Moreover, to evaluate the multivariate model's discrimination, we reported the AUC and its 95% confidence interval, derived from 2,000 bootstrap replicates. We finally proposed a clinical

score from the multivariate analysis by rounding estimates, and we assessed its discrimination performances (AUC, sensibility and specificity for a given threshold). All analyses were performed using R v4.0.2.

The study has been approved by our local ethics committee of Bichat Claude Bernard hospital (CEERB N2019-050).

Results

Patients' demographic characteristics

During the RV and SARS-CoV-2 study periods, 508 and 596 patients were included, respectively. Patients were more frequently male during both periods: 57% (289/508) and 59% (354/596), respectively. The median age was 73 [63–85] years and 60 [46–76] years during the RV and SARS-CoV-2 periods, respectively ($p < 0.001$). Detailed patients' characteristics are depicted in [Table 1](#).

Patients with a negative PCR presented similar characteristics between both periods, except for age—patients were older during the SARS-CoV-2 period (73 [63–85] and 63 [43–72] years, $p < 0.001$)—and cardiac failure, which was more prevalent during the SARS-CoV-2 period (13% vs. 5.8%, $p < 0.002$; [Table 1](#)). Due to these few but significant differences between the two negative-PCR populations from the two periods, we conducted separate analyses of the factors associated with a positive PCR for any RV (in the RV period) and SARS-CoV-2 (in the SARS-CoV-2 period) in comparison with their own PCR-negative populations.

Virological findings

During the first study period, 216/508 (43%) patients had a positive mPCR, including 13 dual viral coinfections, leading to the following viral distribution: 68 (31%) rhinovirus, 60 (28%) influenza, 35 (16%) RSV, 30 (14%) human metapneumovirus, 28 (13%) coronaviruses, four (2%) parainfluenza, three (0.1%) adenovirus and one (0.5%) bocavirus. During the second study period, 268/596 (45%) patients had a positive PCR for SARS-CoV-2, and 70 other respiratory viral infections were also identified, including 18 co-infections with SARS-CoV-2. As patients' populations presented some differences across the two periods, patients with a non-SARS-CoV-2 virus were analyzed as SARS-CoV-2-negative patients, while those with a SARS-CoV-2 co-infection were considered as SARS-CoV-2-positive.

Patients' characteristics associated with the detection of a non-SARS-CoV-2 respiratory virus

The median duration of symptoms was 2 [1–4] days before ED admission. The following characteristics were associated with a positive mPCR in the univariate analysis ([Table 1](#)): younger age, presence of fever, cough, and expectorations, and lower white blood cell and platelet counts. These variables were also retrieved in the multivariate analysis, except for lower white blood cell count ([Table 2](#)).

Clinical and biological characteristics associated with the detection of SARS-CoV-2

The median duration of symptoms was 3 [2–7] days, and the following characteristics were associated with a positive SARS-CoV-2 PCR in the univariate analysis ([Table 1](#)): male gender, younger age, fever, chills, myalgia, cough, bilateral cracklings, diabetes, chronic lung disease, history of stroke, higher respiratory rate, CRP, lower NT-proBNP, lower leukocytes and lymphocytes counts and lower platelet count. Regarding comorbidities, chronic lung disease,

Table 1. Factors associated with a positive PCR for both periods (univariate logistic regression, *p for diff measures statistical significance for the difference between two estimated OR).

		RV period					SARS-CoV-2 period					p for diff*
		Overall (N = 508)	PCR+ (N = 203)	PCR- (N = 305)	OR (95% CI) for PCR+	p	Overall (N = 596)	PCR+ (N = 268)	PCR- (N = 328)	OR (95% CI) for PCR+	p	
General	Male gender	289 (57)	114 (56)	172 (56)	1.0 (0.7–1.4)	0.99	354 (59)	190 (71)	164 (50)	2.4 (1.7–3.4)	<0.001	0.00042
	Age	73 (61–85)	70 (59–82)	73 (63–85)	1.0 (1.0–1.0)	0.02	60 (46–76)	59 (49–73)	62 (43–78)	1.0 (1.0–1.0)	0.54	0.16
	Symptoms duration (days)	2 (1–4)	3 (1–4)	2 (1–4)	1.0 (1.0–1.0)	0.63	3 (2–7)	4 (3–7)	3 (1–7)	1.0 (1.0–1.0)	0.85	0.62
Symptoms	Feverishness	208 (41)	102 (50)	105 (34)	2.0 (1.4–2.8)	<0.001	373 (63)	215 (80)	158 (48)	4.4 (3.0–6.4)	<0.001	0.0026
	Hypothermia	21 (4.2)	6 (3)	14 (5)	0.6 (0.2–1.6)	0.36	19 (3)	6 (2)	13 (4)	0.6 (0.2–1.4)	0.24	0.84
	Chills	82 (16)	35 (17)	47 (15)	1.2 (0.7–1.9)	0.54	121 (20)	71 (26)	50 (15)	2.0 (1.3–3.0)	<0.001	0.088
	Sweats	38 (7.5)	17 (8)	21 (7)	1.2 (0.6–2.4)	0.52	58 (10)	29 (11)	29 (9)	1.3 (0.7–2.2)	0.42	0.99
	Headaches	28 (5.6)	11 (5)	17 (6)	1.0 (0.4–2.1)	0.95	78 (13)	41 (15)	37 (11)	1.4 (0.9–2.3)	0.15	0.42
	Myalgia	68 (14)	29 (14)	36 (10)	1.3 (0.7–2.1)	0.4	134 (23)	81 (30)	53 (16)	2.2 (1.5–3.3)	<0.001	0.082
	Malaise	40 (7.9)	14 (6)	26 (8)	0.8 (0.4–1.6)	0.52	33 (6)	13 (5)	20 (6)	0.8 (0.4–1.6)	0.51	0.97
	Cough	311 (62)	148 (73)	159 (52)	2.6 (1.8–3.9)	<0.001	402 (67)	199 (74)	203 (62)	1.8 (1.3–2.5)	0.0014	0.16
	Sore Throat	24 (4.8)	12 (6)	11 (4)	1.7 (0.7–4.0)	0.22	41 (7)	21 (8)	20 (6)	1.3 (0.7–2.5)	0.41	0.63
	Dyspnea	392 (78)	148 (74)	240 (79)	0.7 (0.5–1.1)	0.16	345 (58)	147 (55)	198 (60)	0.8 (0.6–1.1)	0.18	0.77
	Expectoration	105 (21)	56 (28)	46 (15)	2.2 (1.4–3.4)	<0.001	39 (7)	12 (5)	27 (8)	0.5 (0.3–1.0)	0.069	<0.001
	Chest pain	69 (14)	25 (12)	43 (14)	0.9 (0.5–1.5)	0.59	43 (7)	15 (6)	28 (9)	0.6 (0.3–1.2)	0.17	0.47
	Bilateral cracklings	120 (24)	54 (27)	65 (21)	1.4 (0.9–2.0)	0.16	92 (15)	53 (20)	39 (12)	1.8 (1.2–2.9)	0.0086	0.34
Comorbidities	Renal failure	59 (12)	25 (13)	34 (11)	1.1 (0.6–1.9)	0.68	28 (5)	14 (5)	14 (4)	1.2 (0.6–2.6)	0.6	0.85
	Diabetes	87 (17)	40 (20)	47 (15)	1.4 (0.8–2.2)	0.2	120 (20)	67 (25)	53 (16)	1.7 (1.1–2.6)	0.0087	0.45
	Chronic lung disease	169 (34)	57 (28)	109 (36)	0.7 (0.5–1.0)	0.075	121 (20)	32 (12)	89 (27)	0.4 (0.2–0.6)	<0.001	0.028
	Myocardial infarction	38 (7.6)	17 (8)	21 (7)	1.2 (0.6–2.4)	0.53	42 (7)	19 (7)	23 (7)	1.0 (0.5–1.9)	0.99	0.65
	Cardiac failure	69 (14)	29 (14)	40 (13)	1.1 (0.7–1.9)	0.69	27 (5)	8 (3)	19 (6)	0.5 (0.2–1.1)	0.11	0.11
	Stroke	51 (10)	24 (12)	27 (9)	1.4 (0.8–2.5)	0.27	27 (5)	7 (3)	20 (6)	0.4 (0.2–0.9)	0.046	0.023
	Metastatic cancer	55 (11)	17 (8)	38 (12)	0.6 (0.3–1.2)	0.15	22 (4)	9 (3)	13 (4)	0.8 (0.3–2.0)	0.69	0.63
	Dementia	43 (8.5)	15 (7)	27 (9)	0.8 (0.4–1.6)	0.57	14 (2)	4 (2)	10 (3)	0.5 (0.1–1.4)	0.22	0.43
	Hemiplegia	6 (1.2)	3 (1)	3 (1)	1.5 (0.3–8.3)	0.61	7 (1)	2 (0.75)	5 (2)	0.5 (0.1–2.3)	0.39	0.33

(Continued)

Table 1. (Continued)

		RV period					SARS-CoV-2 period					p for diff ^a
		Overall (N = 508)	PCR + (N = 203)	PCR- (N = 305)	OR (95% CI) for PCR+	p	Overall (N = 596)	PCR + (N = 268)	PCR- (N = 328)	OR (95% CI) for PCR+	p	
	System disease	7 (1.4)	1 (0.5)	6 (2)	0.2 (0.0–1.5)	0.2	17 (3)	9 (3)	8 (3)	1.4 (0.5–3.7)	0.51	0.15
	Vascular disease	9 (1.8)	3 (2)	6 (2)	0.8 (0.2–2.9)	0.69	17 (3)	7 (3)	10 (3)	0.8 (0.3–2.2)	0.74	0.89
Constants	Respiratory rate (min ⁻¹)	18 (16–24)	18 (17–25)	18 (16–22)	1.0 (1.0–1.0)	0.79	18 (16–23)	20 (16–25)	18 (16–20)	1.1 (1.0–1.1)	<0.001	<0.001
	CRP (mg/L)	52 (16–103)	60 (22–116)	42 (11–98)	1.0 (1.0–1.0)	0.97	54 (10–118)	85 (40–146)	20 (4–84)	1.0 (1.0–1.0)	<0.001	0.029
	NT-proBNP (ng/L)	1796 (521–5034)	1489 (398–6735)	2077 (548–4600)	1.0 (1.0–1.0)	0.16	178 (50–1524)	117 (46–393)	488 (62–2746)	1.0 (1.0–1.0)	0.0035	0.0014
	Leukocytes (G/L)	9 (7–13)	9 (6–12)	10 (7–13)	0.9 (0.9–1.0)	<0.001	8 (6–11)	6 (5–7)	9 (7–12)	0.8 (0.7–0.8)	<0.001	<0.001
	Lymphocytes (G/L)	1 (1–2)	1 (1–2)	1 (1–2)	1.0 (0.9–1.1)	0.92	1 (1–2)	1 (1–1)	1 (1–2)	0.8 (0.6–1.0)	0.042	0.065
	Platelets (G/L)	222 (176–283)	195 (162–260)	239 (183–302)	1.0 (1.0–1.0)	<0.001	212 (165–268)	182 (147–222)	240 (191–295)	1.0 (1.0–1.0)	<0.001	0.023
Outcome	ICU admission	26 (5)	10 (5)	16 (5)	0.9 (0.4–2.1)	0.88	77 (13)	65 (24)	12 (4)	8.4 (4.6–16.8)	<0.001	<0.001
	Intra hospital mortality	15 (3)	6 (3)	9 (3)	1.0 (0.3–2.8)	0.99	76 (13)	52 (19)	24 (7)	3.0 (1.8–5.2)	<0.001	0.063

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diabetes, and a stroke history were associated with a positive SARS-CoV-2 PCR. In the multivariate analysis, the following features remained associated with SARS-CoV-2 detection (Table 2): younger age, male gender, fever, chills, myalgia, higher respiratory rate and absence of chronic lung disease. A positive PCR for SARS-CoV-2 was also associated with ICU admission (OR, 8.4; 95% CI, 4.6–16.8; $p < 0.001$) and with mortality during hospitalization (OR, 3.0; 95% CI, 1.8–5.2; $p < 0.001$).

Table 2. Multivariate analysis for positive PCR for both periods (non-SARS-CoV-2 Respiratory Viruses (RV), and SARS-CoV-2) separately, and for SARS-CoV-2 vs RV in a modeled co-circulation period.

	PCR + during RV period (N = 492)*		PCR + during SARS-CoV-2 period (N = 582)*		SARS-CoV-2 vs other respiratory viruses (overall study period)**	
	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
Age (per 10 years)	0.89 (0.80–1.00)	0.041			0.80 (0.72–0.89)	<0.001
Male gender			2.23 (1.53–3.25)	<0.001	1.64 (1.10–2.44)	0.015
Expectoration	1.70 (1.05–2.75)	0.031			0.13 (0.07–0.26)	<0.001
Fever	1.60 (1.08–2.38)	0.02	3.33 (2.25–4.97)	<0.001	3.27 (2.17–4.94)	<0.001
Chills			1.62 (1.03–2.56)	0.038		
Myalgia			1.72 (1.10–2.70)	0.017		
Cough	2.16 (1.43–3.30)	<0.001				
Diabetes						
Chronic lung disease			0.40 (0.24–0.64)	<0.001	0.40 (0.25–0.64)	<0.001
Respiratory rate (min ⁻¹)			1.06 (1.02–1.09)	<0.001		
Platelets (per 100G/L)	0.69 (0.54–0.85)	<0.001				
Leucocytes (per G/L)	0.97 (0.93–1.01)	0.11				

* Number of patients included in this analysis, excluding patients with missing values

** *i.e.* 40 and 45% for non-SARS-CoV-2 viruses and SARS-CoV-2, respectively

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Comparison of human respiratory viruses and characteristics associated with SARS-CoV-2

Under the hypothesis of SARS-CoV-2 co-circulation along with other RVs, variables associated with the virologic diagnosis (SARS-CoV-2 vs other viruses) among positive PCR were as follows (Table 2): male gender (aOR, 1.64; 95% CI, 1.10–1.44; $p = 0.015$), absence of chronic lung disease (0.40, 0.25–0.64, <0.001), age (0.80 per 10 years, 0.72–0.89, <0.001), presence of fever (3.27, 2.17–4.94, <0.001) and absence of expectorations (0.13, 0.07–0.26, <0.001). A clinical score based on this multivariate analysis was computed using integer coefficients based on OR logarithms (S2 Table), ranging from -6 to +5. Under the baseline scenario conditions, corresponding to the overall period of the study with a prevalence of 43% of positive PCR and distribution of 56% and 44% of SARS-CoV-2 and non-SARS-CoV-2 viruses, respectively, among positive PCR, our score has an AUC of 0.81 (95% CI 0.77–0.85; S1 Fig). Furthermore, when using a score greater than 1 to predict SARS-CoV-2 among all viral infections, we observed sensitivity and a specificity of 83% and 65%, respectively. To note, with a score greater than or equal to 1, the sensitivity and specificity were at 91% and 52%, respectively.

To test our observations' robustness in case of variable prevalence of SARS-CoV-2 among all RVs, two other scenarios were added, assuming the same global positivity rate of 43% with a dominant or a limited SARS-CoV-2 distribution circulation among positive PCR at 75% and 25%, respectively. The following factors were associated with COVID-19 diagnosis in all scenarios: younger age, male gender, fever, myalgia, dyspnea, absence of expectoration, and absence of chronic lung disease (Cf. S1 Table). The positive predictive value (PPV) and the negative predictive value (NPV) with a score greater than one were at 75 and 76% with the viral distribution observed in our study. Under the dominant and the limited SARS-CoV-2 distribution scenarios (i.e., 75% and 25% probability of SARS-CoV-2 among positive patients), the PPVs were at 92% and 57%, respectively, and the NPVs were at 45 and 88%, respectively.

Discussion

In this large monocentric prospective cohort study, including 508 and 596 consecutive ILI patients attending the ED during the RV and SARS-CoV-2 periods, respectively, we identified several clinical features associated with positive viral PCR. This allowed us to identify the highest COVID-19 suspicions among all respiratory viral infections.

The ability to distinguish COVID-19 from other RVs will become an increasingly important issue in northern-hemisphere countries as circulation of SARS-CoV-2 could be expected to continue during the upcoming year and the next epidemic of winter-associated viruses [5]. The importance of such co-circulation is challenging to predict. Few countries in the southern hemisphere are currently describing high co-circulation of other RVs with SARS-CoV-2. However, several countries at the beginning of the SARS-CoV-2 outbreak in Northern America or Europe reported such co-circulation [6, 7].

The features observed in our cohort for COVID-19 patients are in line with previous reports [14]. Most of these clinical features are also associated with other respiratory viral infections observed in our study and previous works [15, 16]. By analyzing the comparative strength of these clinical features associations with SARS-CoV-2 positivity in relation to other RVs, we were able to define a limited set of markers associated with a higher risk of being infected by SARS-CoV-2: being male, of a younger age, with feverishness and in the absence of expectoration is predictive of a SARS-CoV-2 infection while having chronic lung diseases is predictive of non-SARS-CoV-2 RVs. Our results were confirmed under several SARS-CoV-2 prevalence conditions and are in line with the only other study available to date comparing features associated with SARS-CoV-2 to those associated with other respiratory viral infections.

Cardiovascular diseases also seem to be associated to SARS-CoV-2 diagnosis, in our model under the different scenarios. This observation is also in line with previous publications that have considered cardiovascular diseases as a biomarker for an increased risk of COVID-19 infection and poor outcomes with a case fatality rate of 10.5% [17, 18].

A small French cohort has also described anosmia, dysgeusia, diarrhea, frontal headache, and bilateral crackling sounds more frequently associated with COVID-19 than other RVs [19]. Our results confirm the findings of this smaller retrospective work on a large prospective cohort, except for diarrhea, which was not associated with COVID-19 diagnosis in our population. In both this previous work and our study, no biological findings upon ED admission allowed for discrimination between SARS-CoV-2 and non-SARS-CoV-2 respiratory infections. An interesting point highlighted in our work is the impact of SARS-CoV-2 and the other RVs relative prevalence on the clinical scoring with PPVs ranging from 57 to 92% and NPVs ranging from 45 to 88% depending on the proportion of SARS-CoV-2 among RVs. As that relative prevalence cannot be predicted and will probably evolve during the RV epidemic period, any clinical scoring of COVID-19 suspicion will have to be monitored in real time and will not eliminate the need for rapid molecular assays.

Our study presents several limitations. First, it is a monocentric study, and the RV period was designed before the emergence of SARS-CoV-2 for analysing other RV features. Therefore, a few key characteristics, such as diarrhea, anosmia, and ageusia, or procalcitonin, which was initially not known to be associated with COVID-19, could not be included in the present work. Their collection could help in future works to improve the clinical scoring of COVID-19 suspicions. As the French COVID-19 initial outbreak began at the end of the winter season, a few other RVs were identified during the SARS-CoV-2 period, alone or in association with SARS-CoV-2. The small numbers of co-infections observed in our work did not allow for an individual assessment of their clinical and biological presentations. Finally, the proposed clinical score requires an external validation before being used for patient management. Moreover, the identified features may evolve in the upcoming years with the ongoing immunization of the general population. Surveillance of the evolution of the disease will, therefore, be required in the future.

In conclusion, symptoms associated with SARS-CoV-2 and other respiratory viral infections are frequently shared [8]. This poses potential challenges in patient management in case of a large co-circulation of all these viruses, as expected in the upcoming months in most northern countries. Despite this overlap, COVID-19 patients present several clinical characteristics less frequently identified among those infected by other RVs such as influenza. Based on this data, we developed a clinical tool to aid in screening SARS-CoV-2 infection among all viral respiratory infections. These observations were confirmed in various ratios of SARS-CoV-2 and other RVs. As having an efficient, reliable, and rapid patient's triage system upon ED entrance, clinical scoring could be a tempting and useful tool depending on one's local environment and constraints, mainly due to the considerable PCR turnaround time or low single room availability either in the ED or in the hospital. However, this tool needs to be prospectively evaluated before any potential use, and, as we demonstrated, the performances may be strongly impacted by the relative prevalence of SARS-CoV-2 and other RVs. As this relative prevalence is impossible to predict soon, no clinical scoring will waive the need for molecular assays. Therefore, on the eve of the next respiratory viruses epidemic period, our primary efforts should still focus on having a large availability, accessibility, and optimized use of rapid molecular testing.

Supporting information

S1 Fig. ROC curves of the multivariate model of RV period (left, N = 492), SARS-CoV-2 period (middle, N = 582) and of the clinical score for SARS-Cov-2 discrimination (right,

N = 463).
(DOCX)

S1 Table. Factors associated with a positive PCR for SARS-CoV-2 given that the PCR is positive to at least one respiratory virus (modeling under different scenarios, univariate analysis; baseline scenario corresponds to the union of both samples, low and high COVID scenario).
(DOCX)

S2 Table. The clinical score for SARS-CoV-2 suspicion w.r.t. other respiratory viruses. A score strictly greater than one has a sensitivity of 83% and a specificity of 65% of presenting a SARS-CoV-2 instead of any other respiratory viruses in case of positive PCR.
(DOCX)

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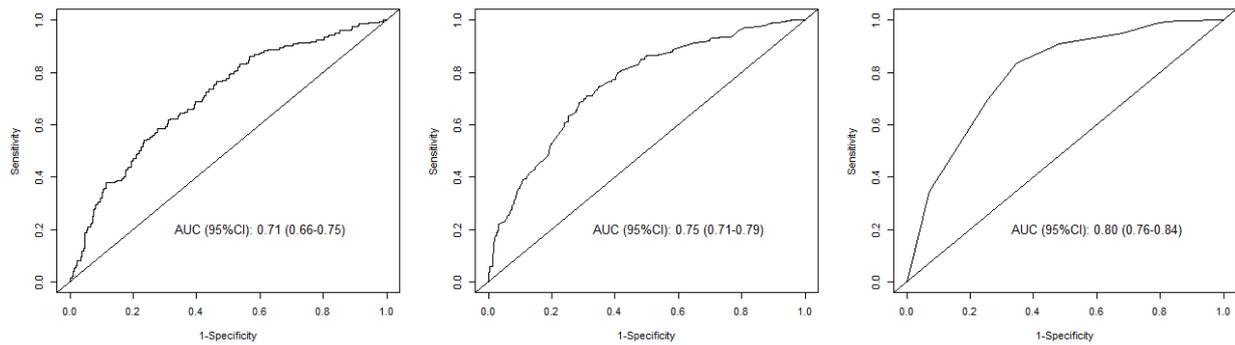
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S1 Fig. ROC curves of the multivariate model of RV period (left, N=492), SARS-CoV-2 period (middle, N=582) and of the clinical score for SARS-CoV-2 discrimination (right, N=463).

Co-circulation scenario		Low COVID scenario		Baseline scenario		High COVID scenario	
		positive PCR 43%		positive PCR 43%		positive PCR 43%	
		SARS-CoV-2 proportion 25%		SARS-CoV-2 proportion 56%		SARS-CoV-2 proportion 75%	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
General	Sex: male	2.29 (1.47-3.58)	0.00027	1.85 (1.27-2.70)	0.0015	1.63 (1.06-2.50)	0.025
	Age	0.97 (0.96-0.98)	1.9e-07	0.97 (0.96-0.98)	1.00E-06	0.98 (0.97-0.99)	0.00014
	Symptoms duration (days)	1.05 (1.01-1.09)	0.01	1.05 (1.01-1.10)	0.0098	1.06 (1.01-1.11)	0.025
Symptoms	Fever	6.60 (4.05-10.75)	3.6e-14	3.88 (2.61-5.75)	1.6e-11	2.83 (1.83-4.38)	2.8e-06
	Hypothermia	0.54 (0.15-2.01)	0.36	0.71 (0.24-2.07)	0.53	0.82 (0.24-2.77)	0.75
	Chills	2.13 (1.29-3.53)	0.0033	1.69 (1.06-2.70)	0.027	1.50 (0.87-2.59)	0.14
	Sweats	1.48 (0.73-3.00)	0.28	1.31 (0.69-2.49)	0.41	1.22 (0.58-2.58)	0.6
	Headaches	3.39 (1.71-6.73)	0.00048	3.11 (1.55-6.25)	0.0014	2.97 (1.27-6.98)	0.012
	Myalgia	3.22 (1.95-5.34)	5.4e-06	2.43 (1.50-3.94)	0.00031	2.09 (1.18-3.72)	0.012
	Malaise	0.60 (0.24-1.51)	0.28	0.68 (0.32-1.45)	0.32	0.73 (0.31-1.70)	0.46
	Cough	1.49 (0.94-2.38)	0.093	0.98 (0.65-1.47)	0.93	0.78 (0.49-1.24)	0.3
	Sore Throat	1.59 (0.69-3.66)	0.27	1.28 (0.59-2.74)	0.53	1.12 (0.46-2.71)	0.8
	Dyspnea	0.36 (0.23-0.56)	5.00E-06	0.41 (0.28-0.62)	2.00E-05	0.45 (0.28-0.72)	0.00095
	Expectoration	0.13 (0.05-0.30)	4.1e-06	0.12 (0.06-0.22)	1.7e-11	0.11 (0.06-0.20)	3.00E-12
	Chest pain	0.35 (0.15-0.80)	0.013	0.41 (0.21-0.78)	0.0064	0.44 (0.22-0.89)	0.022
	Bilateral cracklings sounds	0.85 (0.50-1.43)	0.54	0.66 (0.42-1.04)	0.07	0.58 (0.35-0.95)	0.031
Comorbidities	Renal failure	0.42 (0.17-1.02)	0.056	0.39 (0.19-0.78)	0.0075	0.37 (0.18-0.77)	0.0078
	Diabetes	1.69 (1.02-2.79)	0.042	1.34 (0.85-2.11)	0.21	1.18 (0.70-1.99)	0.54
	Chronic respiratory failure	0.24 (0.13-0.43)	1.7e-06	0.33 (0.21-0.52)	2.1e-06	0.41 (0.25-0.66)	0.00032
	Myocardial infarction	0.88 (0.39-1.97)	0.75	0.82 (0.41-1.64)	0.58	0.79 (0.36-1.73)	0.56
	Heart failure	0.16 (0.06-0.47)	0.00086	0.18 (0.09-0.39)	1.2e-05	0.20 (0.09-0.42)	2.7e-05
	Stroke	0.18 (0.06-0.56)	0.0031	0.20 (0.09-0.44)	8.3e-05	0.21 (0.09-0.47)	0.00015
	Metastatic cancer	0.32 (0.11-0.90)	0.032	0.38 (0.17-0.84)	0.017	0.41 (0.18-0.97)	0.041
	Dementia	0.15 (0.03-0.65)	0.011	0.18 (0.06-0.52)	0.0014	0.21 (0.08-0.58)	0.0027
	Hemiplegia	0.48 (0.05-4.43)	0.51	0.50 (0.09-2.84)	0.43	0.51 (0.08-3.33)	0.48
	System disease	5.15 (1.14-23.26)	0.033	6.94 (1.11-43.40)	0.038	7.83 (0.67-91.70)	0.1
	Vascular disease	1.56 (0.39-6.24)	0.53	1.77 (0.47-6.66)	0.4	1.89 (0.38-9.40)	0.44
Constants	Temperature (C°)	1.94 (1.60-2.36)	1.7e-11	1.64 (1.40-1.91)	4.1e-10	1.49 (1.26-1.75)	1.9e-06
	Respiratory rate (min ⁻¹)	1.03 (1.00-1.06)	0.058	1.01 (0.99-1.04)	0.3	1.01 (0.98-1.04)	0.69
	C Reactive Protein (mg/L)	1.00 (1.00-1.01)	0.14	1.00 (1.00-1.01)	0.41	1.00 (1.00-1.01)	0.65
	NT-proBNP (ng/L)	1.00 (1.00-1.00)	0.00046	1.00 (1.00-1.00)	8.8e-07	1.00 (1.00-1.00)	3.4e-07
	Leukocytes (G/L)	0.78 (0.62-0.98)	0.031	0.84 (0.79-0.90)	4.1e-07	0.88 (0.84-0.93)	5.1e-06
	Lymphocytes (G/L)	0.70 (0.00-NA)	0.98	0.87 (0.62-1.21)	0.4	0.96 (0.83-1.10)	0.56
	Platelets (G/L)	0.99 (0.99-1.00)	6.4e-06	1.00 (0.99-1.00)	0.0012	1.00 (1.00-1.00)	0.088
Outcome	ICU admission	10.73 (5.58-20.63)	1.1e-12	6.17 (3.04-12.51)	4.6e-07	4.91 (2.04-11.83)	4.00E-04
	Intra hospital mortality	10.75 (4.93-23.41)	2.3e-09	7.89 (3.28-18.98)	4.0e-06	6.81 (2.25-20.61)	0.00069

S1 Table. Factors associated with a positive PCR for SARS-CoV-2 given that the PCR is positive to at least one respiratory virus (modeling under different scenarios, univariate analysis; baseline scenario corresponds to the union of both samples, low and high COVID scenario)

OR: odd ratio for SARS-CoV-2 detection among positive PCR

Variable	score
Fever	2
Age < 60	2
Sex (male)	1
Chronic lung disease	-2
Expectoration	-4

S2 Table. The clinical score for SARS-CoV-2 suspicion w.r.t. other respiratory viruses. A score strictly greater than one has a sensitivity of 83% and a specificity of 65% of presenting a SARS-CoV-2 instead of any other respiratory viruses in case of positive PCR.

Épidémiologie virale et co-infections du SARS-CoV-2 avec d'autres virus respiratoires lors de la première vague COVID-19 à Paris, France

Contexte et objectif

En mars 2021, la COVID-19 a déjà été responsable de plus de 117 millions d'infections et de plus de 2,6 million de décès dans le monde [43]. Les symptômes courants de la COVID-19 sont la fièvre, la toux, la dyspnée, la fatigue, les myalgies et la diarrhée. La plupart de ces symptômes entrent également dans la définition du syndrome grippal [46,62]. En France, la première vague du SARS-CoV-2 a frappé de fin février à fin avril 2020, coïncidant avec la toute fin de l'épidémie de virus associés à l'hiver cette année et soulevant la question des co-infections virales potentielles avec le SARS-CoV-2 et leur impact.

Quelques études ont rapporté des cas de co-infections SARS-CoV-2 avec d'autres virus respiratoires, et une méta-analyse a estimé la prévalence de ces co-infections virales à 3% [78,84,85]. Cependant, aucune des études n'a utilisé des méthodes de mPCR systématiques à large spectre. De plus, il n'y a pas de données sur l'impact de la co-infection virale SARS-CoV-2 sur la gravité de la maladie et les résultats cliniques.

Ici, nous profitons de la réalisation systématique de la PCR multiplex (mPCR) des patients hospitalisés pour infection des voies respiratoires lors de la première vague épidémique de SARS-CoV-2 pour évaluer la co-circulation de tous les virus respiratoires avec le SARS-CoV-2, le nombre de co-infections virales avec le SARS-CoV-2, et les caractéristiques cliniques de ces co-infections.

Méthodes

Tous les patients adultes hospitalisés dans un hôpital de première ligne COVID-19 à Paris, France, du 25 janvier 2020 au 30 avril 2020 ont été inclus. Tous ont été testés par des tests mPCR systématiques s'ils présentaient des symptômes de syndrome grippal (SG), selon la définition eCDC, et nécessitaient une hospitalisation. Les deux mPCR utilisées au cours de la période d'étude, le panel respiratoire QIAstat-Dx SARS-CoV-2, Qiagen [86], et le BioFire FilmArray RP2 +, BioMérieux [31] permettent de détecter une large gamme de cibles respiratoires virales et les bactéries atypiques. Selon la définition nationale française, une RT-

PCR spécifique pour le SARS-CoV-2 a été réalisée pour tous les patients à risque à partir du 10 mars 2020. Au cours de cette période, trois tests SARS-CoV-2 RT-PCR ont été utilisés: le test RT-PCR recommandé par l'OMS, le kit RealStar® SARS-CoV-2 RT-PCR (Altona, Allemagne) et le Cobas® assay SARS-CoV-2 (Roche Diagnostics, USA). Tous ces tests ont fourni des performances et une limite de détection similaires [87,88]. Les caractéristiques démographiques, cliniques et biologiques ont été collectées de manière prospective au service d'accueil des urgences et rétrospectivement auprès des autres unités. Les caractéristiques de base de chaque groupe ont été résumées à l'aide de statistiques descriptives appropriées.

Résultats

3768 patients ont été inclus pendant la période d'étude, 1906 du service d'accueil des urgences et 1862 autres patients hospitalisés dans les étages. Dans l'ensemble, 806 (21%), 755 (20%) et 28 (1%) échantillons étaient respectivement positifs pour le SARS-COV-2, tout autre virus respiratoire ou une bactérie atypique. A la date de la première vague de SARS-COV-2, les rhinovirus, les coronavirus humains, les adénovirus ou les virus parainfluenza circulaient encore, mais l'essentiel de l'épidémie de virus respiratoires saisonniers avaient déjà disparu, en particulier les virus influenza (cf Figure 5). Parmi les 806 patients positifs pour le SARS-COV-2 étaient co-infectés, respectivement, par un seul autre virus (n= 42, 5%), deux autres virus (n=7 1%) ou une des bactéries atypiques (n= 6, 1%). Les virus les plus fréquemment associés au SARS-COV-2 étaient les rhinovirus (17), les coronavirus humains courants (15), les adénovirus (7), les parainfluenza (5), les métapneumovirus (4), les influenza (4) et le RSV (2) et d'autres agents pathogènes (7). La distribution temporelle des agents pathogènes est illustrée ci-dessous. Les patients consultant aux urgences atteints du SARS-COV-2 seul (n = 249) ou co-infectés avec un autre virus respiratoire (n = 33) présentaient un âge, des symptômes, des constantes vitales ou des comorbidités similaires, à l'exception de la fièvre (p = 0,013) plus fréquentes chez les mono-infectés et des céphalées (p = 0,048) plus fréquentes chez les patients avec des co-infections virales. Parmi ces patients co-infectés, aucun n'a été hospitalisé en unité de soins intensifs contre 64/249 (26%) patients avec seulement une infection par le SARS-COV-2 (p = 0,78). 5 (2%) parmi les patients co-infectés sont décédés pendant l'hospitalisation, et 49 (20%) dans le groupe des mono-infectés par le SARS-CoV-2 (p = 0,48).

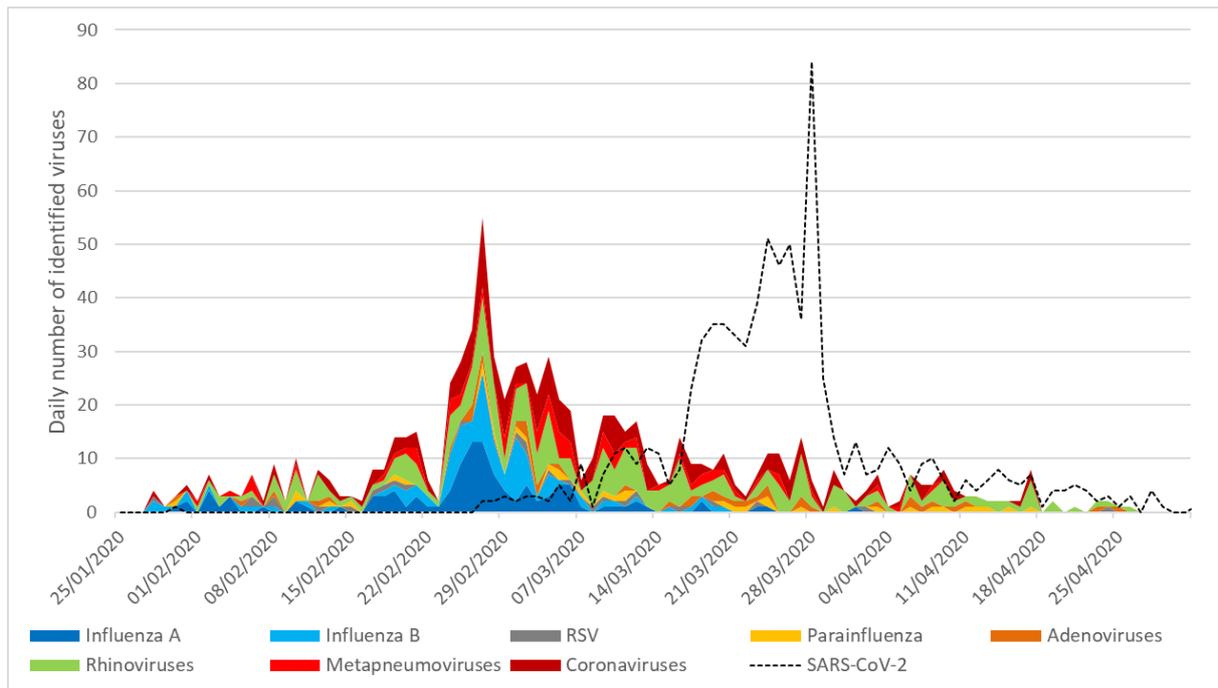


Figure 5 Distribution temporelle du SARS-CoV-2 et des autres virus respiratoires pendant la période de l'étude

Discussion

Ce travail a permis de mettre en évidence que 6% des patients infectés par le SARS-CoV-2 présentaient une co-infection virale dans notre hôpital. Cette proportion est plus élevée que précédemment rapportée pour le SARS-CoV-2 [85] mais à un niveau similaire à celui des co-infections retrouvées pour les autres virus respiratoires [17]. Cette forte prévalence de co-infections virales a été observée malgré la circulation limitée d'autres virus respiratoires en raison du confinement, du couvre-feu et du fait d'être en fin de saison des virus respiratoires [84]. Les rhinovirus, adénovirus et autres coronavirus étaient les virus les plus fréquemment détectés avec le SARS-CoV-2. Des adénovirus et rhinovirus ont déjà été signalés, en dehors du champ d'application du SARS-CoV-2, comme étant plus fréquemment impliqués dans la co-infection virale, contrairement aux virus grippaux [89].

Dans notre cohorte, les patients présentant des co-infections virales avec le SARS-CoV-2 avaient des tableaux cliniques similaires, à l'exception des céphalées et de la fièvre, et un pronostic similaire.

Notre étude présente plusieurs forces et limites. Elle a montré un nombre relativement important de co-infections SARS-CoV-2 par rapport aux travaux précédents [78,85,90] et a mis en relation des données virologiques avec des données cliniques détaillées. Un test mPCR syndromique a été réalisé sur tous les patients présentant un syndrome grippal au cours de la

période d'étude. Ainsi, les patients recrutés dans cette étude observationnelle ne sont pas biaisés vers des patients plus sévères et représentent l'ensemble des patients adultes hospitalisés pour syndrome grippal. Cependant, notre étude est monocentrique, et l'épidémie de SARS-CoV-2 s'est déclarée en Ile-de-France alors que l'incidence de la plupart des virus respiratoires diminuait. La prévalence des co-infections virales avec le SARS-CoV-2 pourrait être plus élevée dans des scénarios avec une circulation active de virus respiratoires et / ou une fois que les mesures barrières seront moins suivies ou abandonnées. Ainsi, bien que nous ayons constaté que les co-infections virales SARS-CoV-2 étaient rares au cours de la première vague épidémique et ne différaient ni par leur présentation clinique ni par leur pronostic des mono-infections SARS-CoV-2, ce constat rassurant devra être confirmé à l'avenir.

Au total, ce travail montre que les co-infections virales restent rares même avec le SARS-CoV-2 et le tableau clinique et leur pronostic de ces patients n'est pas plus sévère. Ces données sont à confirmer dans les années à venir.

Viral epidemiology and SARS-CoV-2 co-infections with other respiratory viruses during the first COVID-19 wave in Paris, France

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Abstract

Objectives: Our work assessed the prevalence of co-infections in patients with SARS-CoV-2.

Methods: All patients hospitalized in a Parisian hospital during the first wave of COVID-19 were tested by multiplex PCR if they presented ILI symptoms.

Results: A total of 806 patients (21%) were positive for SARS-CoV-2, 755 (20%) were positive for other respiratory viruses. Among the SARS-CoV-2-positive patients, 49 (6%) had viral co-infections. They presented similar age, symptoms, except for fever ($P = .013$) and headaches ($P = .048$), than single SARS-CoV-2 infections.

Conclusions: SARS-CoV-2-infected patients presenting viral co-infections had similar clinical characteristics and prognosis than patients solely infected with SARS-CoV-2.

KEYWORDS

respiratory viruses, SARS-CoV-2, syndromic testing, viral co-infection

1 | INTRODUCTION

As of December 2020, COVID-19 has been responsible for more than 63 million infections and over 1.5 million deaths worldwide.¹ The common symptoms of COVID-19 are fever, cough, dyspnea, fatigue, myalgia, and diarrhea. Most of these symptoms are also falling within the definition of influenza-like illness (ILI).^{2,3} In France, SARS-CoV-2 first wave struck from late February to the end of April, coinciding with the very end of the winter-associated viruses' epidemic this year and raising the question of potential viral co-infections with SARS-CoV-2 and their impact.

A few studies reported cases of SARS-CoV-2 co-infection with other respiratory viruses, and a meta-analysis estimated the prevalence of those viral co-infections to 3%.⁴⁻⁷ However, none of the included studies has used systematic wide range PCR methods. Moreover, there are no data on the impact of SARS-CoV-2 viral co-infection on disease severity and clinical outcomes.

Here, we take advantage of the systematic multiplex PCR (mPCR) testing of patients hospitalized for respiratory tract infection during the first SARS-CoV-2 epidemic wave to assess the cocirculation of

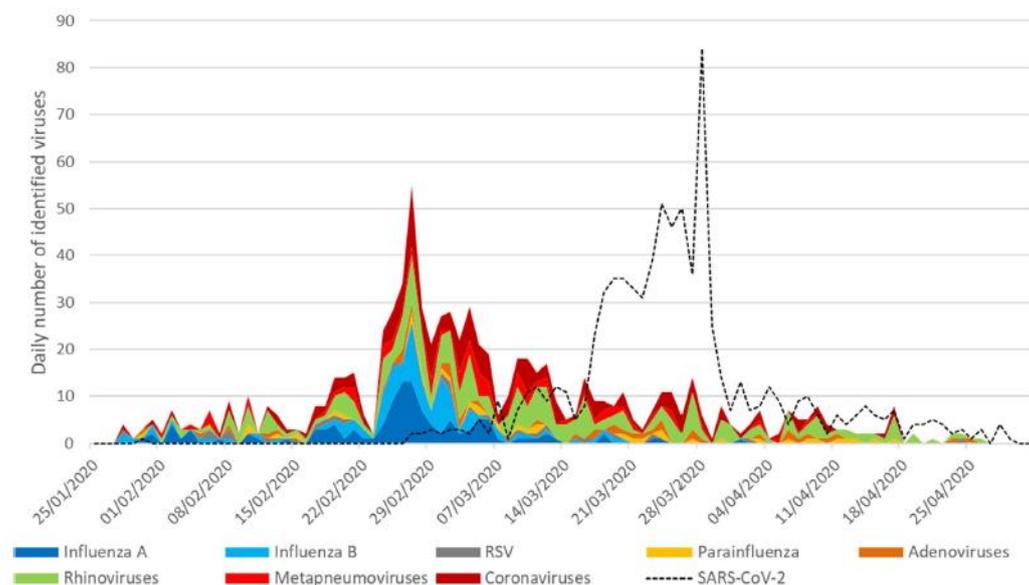
Quentin Le Hingrat and Donia Bouzid equally contributed to this work.

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TABLE 1 Main clinical characteristics of patients presenting a SARS-CoV-2 infection with or without any other respiratory virus co-infection

	SARS-CoV-2 only (n = 249)	SARS-CoV-2 co-infection with another respiratory virus (n = 33)	P- value
Age (median, IQR)	59 (49-73)	58 (45-69)	.26
Male gender	175 (70%)	24 (73%)	.84
Fever	202 (81%)	21 (64%)	.037
Dyspnea	137 (55%)	16 (48%)	.57
Expectoration	10 (5%)	2 (10%)	.6
Cough	184 (74%)	22 (67%)	.4
Myalgia	74 (30%)	10 (30%)	1
Headache	36 (14%)	10 (30%)	.04
Symptoms duration, median (IQR)	4 [3-7]	3 [2-7]	.26
ICU admission, day 1	64 (26%)	0 (0%)	<.001
ICU admission, day 14	31 (15%)	3 (9%)	.27
Hospital mortality	49 (20%)	5 (15%)	.48

**FIGURE 1** Temporal distribution of SARS-CoV-2 and other respiratory viruses during the study period

all respiratory viruses with SARS-CoV-2, the number of SARS-CoV-2 viral co-infections, and the clinical features of such co-infections.

2 | METHODS

All adult patients hospitalized in a COVID-19 first-line hospital in Paris, France, from January 25, 2020, to April 30, 2020, were included. All patients were tested by systematic mPCR testing if they

presented ILI symptoms, according to the eCDC definition, and required hospitalization. The two mPCR assays used during the study period, the QIAstat-Dx SARS-CoV-2 respiratory panel, Qiagen,⁸ and the BioFire FilmArray RP2+, BioMérieux,⁹ allow for detecting a wide range of viral and atypical bacterial respiratory targets, including influenza A and B, parainfluenza virus, rhinoviruses/enteroviruses, RSV, metapneumovirus, adenovirus, human coronaviruses (229E, HKU1, OC43, and NL63), *Mycoplasma pneumoniae*, and *Bordetella pertussis*. According to the French national definition, a specific

SARS-CoV-2 RT-PCR for at-risk patients was performed, starting from March 10, 2020, when systematic testing for SARS-CoV-2 infection began. During this period, three SARS-CoV-2 RT-PCR assays were used: the WHO-recommended in-house RT-PCR assay, the RealStar® SARS-CoV-2 RT-PCR kit, and the Cobas® SARS-CoV-2 assay (Roche Diagnostics). All these assays provided similar performance and limit of detection.^{10,11} Demographic, clinical, and biological features were prospectively collected in the Emergency Department (ED) and retrospectively from the other units. Baseline characteristics within each group were summarized using appropriate descriptive statistics. The statistical analysis was performed using Stata15. The research was approved by the local ethic committee N° CER2020-6 (Table 1).

3 | RESULTS

A total of 3768 patients were included during the study period, 1906 from the ED and 1862 other inpatients. Overall, 806 (21%), 755 (20%), and 28 (1%) samples were positive for SARS-CoV-2, any other respiratory viruses, or atypical bacteria, respectively. The SARS-CoV-2 wave struck from February to April with a peak incidence between mid-March and early-April. At this time, rhinoviruses, human coronaviruses, adenoviruses, or parainfluenza viruses were still circulating, but most of the seasonal respiratory virus epidemic was already gone, especially influenza (cf Figure 1). Among the 806 SARS-CoV-2-positive patients, 42 (5%), 7 (1%), and 6 (1%) also presented one virus, two other viruses, and atypical bacteria, respectively, and 61 (8%) non-SARS-CoV-2 patients positive by mPCR showed viral co-infections. Most frequently associated viruses were rhinoviruses (17), common human coronaviruses (15), adenoviruses (7), parainfluenza (5), metapneumovirus (4), influenza (4), and RSV (2), and other pathogens (7). The temporal distribution of pathogens is depicted below (Figure 1). When comparing ED patients with SARS-CoV-2 either alone ($n = 249$) or associated ($n = 33$), they presented similar age, symptoms, vital signs measurements, or comorbidities, except for fever ($P = .013$) and headaches ($P = .048$) (Table 1). Among those co-infected patients, 0 (0%) were hospitalized in ICU at day 1 versus 64/249 (26%) patients with only a SARS-CoV-2 infection, $P = .78$. 5 (2%) among the co-infected patients died during hospitalization, and 49 (20%) with only a SARS-CoV-2 infection, $P = .78$.

4 | DISCUSSION

This work highlights that 6% of SARS-CoV-2-infected patient presented with viral co-infection at our adult ED. This proportion is higher than previously reported for SARS-CoV-2⁶ but at a level similar to the other respiratory viruses.¹² This high prevalence of viral co-infections was observed, despite the limited circulation of other respiratory viruses due to lockdown, curfew, and being

in the tail of the season of respiratory viruses.⁷ Rhinoviruses, adenoviruses, and other coronaviruses were the most frequently detected viruses with SARS-CoV-2. Adenoviruses and rhinoviruses have already been reported, outside the scope of SARS-CoV-2, as being more frequently involved in viral co-infection, contrary to influenza viruses.¹³

In our population, only 6 patients with SARS-CoV-2 were also infected with atypical bacteria. Co-infections can lead to viral interference, one virus limiting or suppressing the replication of the second virus, or to an enhancement of disease severity compared to mono-infection.¹⁴ In our cohort, patients presenting with viral co-infections with SARS-CoV-2 had similar clinical pictures, except for headache and fever, and prognosis than patients solely infected with SARS-CoV-2.

Our study presents several strengths and limitations. It showed a relatively large number of SARS-CoV-2 co-infections compared to previous works⁴⁻⁷ and linked virological data with detailed clinical data. Syndromic mPCR testing was performed on all patients presenting with ILI during the study period. Thus, patients recruited in this observational study are not skewed toward more severe patients and represent all adult patients hospitalized for ILI. However, our study is monocentric, and the SARS-CoV-2 epidemic flared in Ile-de-France when the incidence of most respiratory viruses was waning. Prevalence of viral co-infections with SARS-CoV-2 might be higher in settings with an active circulation of respiratory viruses and/or once social distancing will be over. We also cannot rule out that some specific co-infections might have a deleterious impact, notably SARS-CoV-2/influenza, as only 4 were detected during our study period. Higher severity of SARS-CoV-2/influenza A H1N1pdm2009 has recently been described in golden Syrian hamsters when the two viruses were simultaneously inoculated.¹⁵ We also did not retrieve data on the other pneumonia diagnosis related to *pneumococcus* or *staphylococcus*. Thus, although we found that SARS-CoV-2 viral co-infections were rare during the first epidemic wave and did not differ either by their clinical presentation or by their outcome from SARS-CoV-2 mono-infections, this reassuring finding must be confirmed in the upcoming months.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Donia Bouzid: Conceptualization (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Quentin Le hingrat: Conceptualization (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Christophe Choquet: Investigation (equal); Project administration (equal); Writing – original draft (equal). odile Laurent: Investigation (equal); Software (equal). Xavier Lescure: Supervision (equal); Writing – review and editing (equal). Jean François Timsit: Validation (equal); Writing – review and editing (equal). Nadhira Houhou Fidouh: Writing – review and editing (equal). Enrique Casalino: Supervision (equal); Validation (equal); Writing – review and editing (equal). Jean Christophe Lucet: Writing – review and editing (equal). Diane Descamps: Validation (equal); Writing – review and editing (equal). Benoit Visseaux: Supervision (equal); Validation (equal); Writing – review and editing (equal).

TRANSPARENCY DECLARATIONS

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PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/irv.12853>.

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Discussion et perspectives

La pandémie de SARS-CoV-2 aura eu comme impact principal de mettre l'accent sur la nécessité d'un diagnostic virologique rapide et fiable au sein des services d'accueil des urgences. L'instauration rapide des mesures de précaution est la pierre angulaire pour prévenir les épidémies nosocomiales au sein de l'hôpital.

Dans la revue narrative sur les tests de diagnostic rapide pour les maladies infectieuses aux urgences, nous avons constaté que les tests moléculaires étaient fiables et ont montré un impact positif dans certaines pathologies, notamment respiratoires. Par contre, les mPCR délocalisées aux urgences étaient comparées à des procédures de PCR faites au laboratoire qui n'incluaient pas forcément un panel multiplex.

Lors de la première étude rétrospective menée au cours de cette thèse (2015-2018), nous avons vu qu'un délai médian de rendu de résultat de la PCR par le laboratoire de virologie (>18h) ne permettait pas le placement en chambre seule des patients grippés. Les médecins urgentistes prenaient leur décision de placement sans avoir connaissance du résultat de PCR et uniquement 25% des patients grippés se retrouvaient hospitalisés en chambre seule.

Au cours de l'hiver 2018-2019, nous avons mené une étude de faisabilité avec une mPCR délocalisée dont l'utilisation était limitée à quelques médecins et aux patients les plus sévères. Ce travail a montré que l'usage de la mPCR s'intègre bien dans le quotidien de soins aux urgences et a permis de mieux placer les patients grippés en chambre seule avec une prescription plus adaptée d'Oseltamivir.

Suite à ce travail de faisabilité, nous avons monté une étude pragmatique au cours de l'hiver 2019-2020 pour évaluer l'impact de la mPCR réalisée en POCT aux urgences, versus la mPCR réalisée au laboratoire de virologie, en ayant recours à des périodes hebdomadaires alternées. Ce travail a confirmé l'impact positif sur les mesures de précaution et plus précisément sur le placement en chambre seule des patients ayant une PCR positive. Par contre, nous n'avons pas pu montrer une réduction de la durée de séjour hospitalier ni même de la prescription d'antibiotiques.

Le nombre de chambres seules étant limité au sein des hôpitaux, pouvoir les attribuer à bon escient pour les patients infectés par les virus influenza, VRS, métapneumovirus ou SARS-CoV-2 est nécessaire, même si la pratique du cohorting est possible en période de pandémie. Et le fait de pouvoir obtenir une réponse virologique rapide permet une meilleure gestion des lits au sein de l'hôpital.

Au cours de l'hiver 2020, l'émergence du SARS-CoV-2 a bouleversé les pratiques ; à partir du 10 mars 2020, nous étions obligés en France de dépister les patients admis à l'hôpital pour le SARS-CoV-2. Nous avons disposé, au gré des stocks fluctuants, de tests multiplex incluant le SARS-CoV-2 dans le panel respiratoire que nous utilisions déjà en *point of care* aux urgences. Le laboratoire de virologie a aussi élargi ses horaires de travail pour apporter aux praticiens des réponses virologiques, le plus rapidement possible.

Nous avons poursuivi le recueil prospectif des informations relatives aux patients consultants aux urgences avec un syndrome grippal pendant la période du SARS-CoV-2 et ainsi pu déterminer les caractéristiques cliniques plus associées à la COVID-19 qu'aux autres infections respiratoires virales. Nous avons proposé un score clinique simple, qui reste à valider, mais qui a pour objectif de simplifier le tri aux urgences en attendant la confirmation virologique, de plus en plus en rapide.

Nous avons aussi décrit les rares cas de co-infections virales avec le SARS-CoV-2, à des taux supérieurs à ce qui était précédemment décrit, et montré que ces patients présentaient les mêmes présentations cliniques et n'étaient pas plus sévères que ceux qui avaient une mono-infection SARS-CoV-2.

Les techniques délocalisées de diagnostic virologique sont récemment apparues et ont considérablement évolué encore avec l'émergence du SARS-CoV-2. Leur utilisation permet de renforcer considérablement les pratiques d'isolement et la sécurité des soins. Les études précédentes sur le sujet ont montré des résultats contradictoires sur l'impact de la mPCR en *point of care* sur la durée de séjour et la prescription d'antibiotiques, son usage dans notre CHU ne semble pas être suffisant pour montrer un impact sur la durée de séjour ni la prescription d'antibiotiques. Pour aller plus loin et réduire efficacement la durée de séjour et la prescription d'antibiotiques nous pensons que le diagnostic syndromique en *point of care* doit être associé à d'autres marqueurs et outils comme le scanner thoracique ou certains marqueurs biologiques des infections (C-Réactive-Potéine ou procalcitonine) pour permettre d'éliminer la présence d'infection bactérienne sous-jacente à la présence d'un virus respiratoires.

Une étude menée en 2013 combinant le résultat de la PCR à celui de la procalcitonine avait montré une réduction de la prescription d'antibiotiques chez des patients ayant une PCR positive à un virus respiratoire et une procalcitonine inférieure à 0,25 µg/mL. Néanmoins cet effet était aussi retrouvé dans le bras non interventionnel [91].

La place du scanner thoracique dans le diagnostic des pneumonies a été révélé, lors de précédents travaux et confirmé au cours de la pandémie actuelle de SARS-CoV-2, comme étant

un élément clé de la démarche diagnostique[92,93]. La mise en place d'un algorithme combinant la mPCR, les marqueurs de l'inflammation avec le scanner thoracique semble être la piste pour aboutir à un véritable effet sur la prescription d'antibiotiques et la durée de séjour. L'élaboration de cet algorithme nécessite un travail collégial entre urgentistes, médecins infectiologues, virologues, biologistes et radiologues. Cependant, le risque existe d'une non adhésion des médecins aux algorithmes, et des études qualitatives ancillaires à ce projet sont souhaitables afin de déterminer les motifs de non adhésions.

Le recours à la biologie moléculaire, néanmoins, ne reste pas sans risque ; Il y a certains points de vigilance lorsque du personnel sans formation initiale utilise ces méthodes : risque de contamination des échantillons, non-respect des traçabilités dans des services d'urgences souvent surchargés, mauvais suivi des températures de conservation et des stocks...

En effet, la simplicité croissante des technologies, y compris de biologie moléculaire, permet de conserver un niveau de sécurité très satisfaisant. Cependant la présence de référents locaux est nécessaire, pour permettre un dialogue permanent avec les laboratoires et organiser des formations régulières à la technique pour maintenir un niveau de qualité satisfaisant.

Pour conclure des essais contrôlés randomisés sont nécessaires pour évaluer l'impact d'un algorithme intégrant à la fois, la mPCR délocalisée aux urgences, certains marqueurs biologiques et enfin le scanner pour espérer avoir un impact concret sur la durée de séjour et la prescription d'antibiotiques chez les patients ayant des tableaux de pneumonies aiguës communautaires avec une évaluation coût efficacité et une étude sociologique s'intéressant aux pratiques individuelles des médecins prescripteurs.

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