



Modelling COVID-19 spread in educational settings for safe in-person learning

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Modélisation de la propagation de COVID-19 dans les établissements scolaires afin de maintenir l'apprentissage en personne en toute sécurité

par

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Résumé de la thèse en français

Introduction

Les établissements scolaires sont des environnements où un grand nombre d'élèves interagissent étroitement et de manière prolongée dans des espaces clos. De par leur nature, les écoles peuvent créer des conditions favorables à la transmission de virus respiratoires. Les jeunes enfants peuvent jouer un rôle clé dans la propagation de l'infection par le biais des contacts à l'école, ce qui peut à son tour affecter leurs parents et augmenter ainsi les niveaux de transmission globaux dans la communauté. Cela a été le cas lors de la pandémie de grippe H1N1 en 2009, où la transmission au niveau de la population était nettement plus faible lorsque les écoles étaient fermées pendant les vacances et plus élevée lorsque les écoles étaient de nouveau en session [1–4].

Ainsi, les établissements scolaires ont été parmi les premiers établissements à être fermés en réponse à l'explosion de cas dans le monde en mars 2020 [5]. Cependant, la connaissance limitée sur la circulation du SARS-CoV-2 chez les enfants et les adolescents rendait difficile l'identification préventive de l'intervention qui pourrait concilier l'apprentissage en présentiel et le contrôle de la pandémie une fois les écoles rouvertes. De plus, l'évolution du paysage de la pandémie, y compris l'émergence de nouvelles variantes, continuait de poser des défis à la gestion du fonctionnement normal des écoles et à la sélection de stratégies efficaces.

Depuis le début de la pandémie de COVID-19, la modélisation mathématique a offert des projections sur l'évolution de la pandémie et l'impact de mesures telles que les confinements, les couvre-feux et la distanciation sociale, mais une compréhension floue persistait toujours concernant les mécanismes de transmission chez les élèves.

Mon travail de recherche vise à éclairer le rôle de la transmission de la COVID-19 dans les écoles afin de fournir des informations et d'affiner les stratégies de contrôle dans les établissements scolaires, en mettant l'accent sur la santé et la sécurité des enfants pendant les vagues Alpha, Delta et Omicron. J'ai utilisé un modèle basé sur des agents sur des réseaux scolaires empiriques pour proposer des stratégies alternatives à la fermeture des écoles, afin de contraster la propagation virale tout en minimisant les perturbations éducatives. Lorsqu'elles étaient disponibles, les données de dépistage sur le terrain ont été intégrées dans le cadre de modélisation pour reproduire au mieux les conditions épidémiques spécifiques. En m'appuyant sur une approche empirique basée sur les données, je fournis ainsi des perspectives qui pourraient améliorer la capacité des autorités à prendre des décisions fondées sur des preuves et à gérer efficacement la COVID-19 dans les écoles en France.

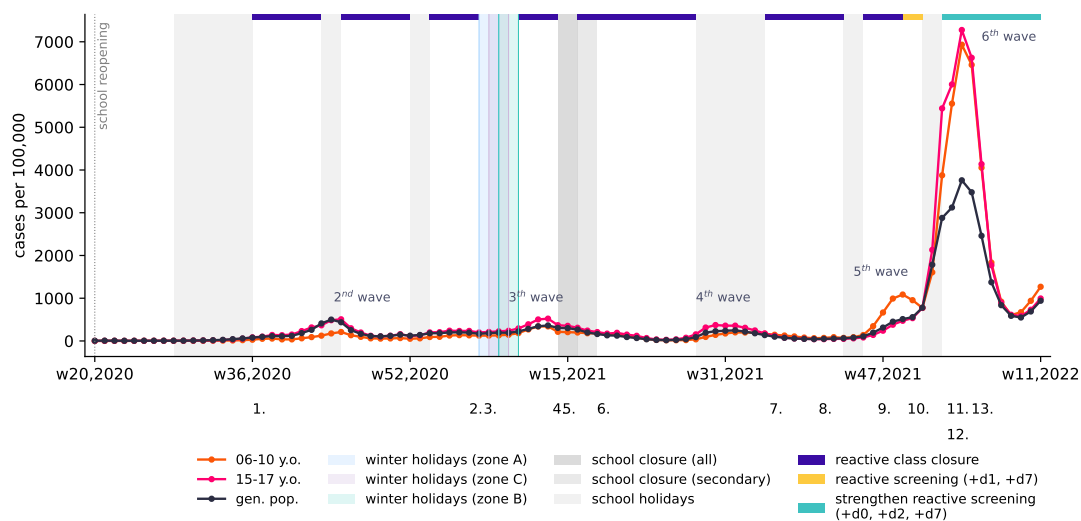


Figure 1: Incidence hebdomadaire en France par classes d'âge et calendrier des protocoles scolaires appliqués dans les écoles primaires de la réouverture des classes en mai 2020 à mars 2022. Les lignes colorées représentent l'incidence hebdomadaire par classe d'âge. Les classes d'âge suivantes sont considérées : 6-10 ans correspondant aux élèves du primaire (en orange) et 15-17 ans correspondant aux élèves du secondaire (en rose). À titre de comparaison, l'incidence hebdomadaire dans la population générale est indiquée en gris foncé. L'incidence hebdomadaire se réfère à la France, y compris les territoires d'outre-mer. Les zones verticales grises correspondent aux jours fériés nationaux ou aux fermetures d'écoles. Les zones verticales colorées correspondent aux jours fériés dans des zones spécifiques en France. Les lignes horizontales en haut représentent les protocoles de dépistage appliqués dans les écoles primaires françaises, allant de *fermeture réactive de l'école*, *dépistage réactif*, *renforcement du dépistage réactif*. Source : Ministère français de l'éducation : Ministère français de l'éducation nationale [6]

Contexte et gestion de la pandémie de COVID-19 dans les établissements scolaires en France

Lorsque le COVID-19 est apparu comme une pandémie mondiale en mars 2020, les établissements scolaires ont été parmi les premiers à être fermés pour freiner la transmission du SARS-CoV-2. Cependant, le choix de fermer les établissements scolaires pendant une période relativement longue a été très controversé et largement débattu, notamment en raison des effets néfastes sur le bien-être des élèves et le développement de l'apprentissage. C'est pourquoi les gouvernements du monde entier ont progressivement réintroduit les activités en personne dans les écoles, en mettant en œuvre diverses mesures de contrôle pour gérer les cas positifs. Les approches adoptées par les différents pays ont varié, certains adoptant des stratégies réactives en réponse aux cas confirmés, tandis que d'autres ont mis en œuvre des mesures plus proactives au fur et à mesure que la pandémie progressait.

En France, les écoles primaires et secondaires ont été fermées lors du premier confinement en France du 17 mars au 10 mai 2020. Depuis le 11 mai 2020, les établissements scolaires ont rouvert progressivement conformément aux protocoles sanitaires du Haut Conseil de la Santé Publique (HCSP). Pour les années suivantes, le principe principal était de promouvoir les cours en présentiel pour tous les élèves pour assurer leur bien-être, tout en limitant la circulation du virus. Les mesures ont été encadrées dans un système hiérarchisé, avec des

niveaux spécifiques déclenchés en fonction du contexte épidémique. En cas de fermeture de classe ou d'école, le plan de continuité pédagogique (cours en ligne, classes virtuelles, etc.) était mis en œuvre. Ce principe a été maintenu tout au long de la pandémie.

Trois différentes stratégies de traçage ont été mises en œuvre dans les établissements scolaire tout au long de la pandémie en France (Figure 1):

- *Fermeture réactive de classe*: Cette mesure a été initialement appliquée au début de l'année scolaire en septembre 2020 et a été réitérée avec quelques modifications jusqu'en décembre 2021. Elle impliquait principalement la fermeture de la classe après l'identification d'un cas positif confirmé et la fermeture de l'école après la confirmation de trois cas positifs dans la même classe. L'isolement des cas confirmés et la fermeture de la classe duraient 7 jours.
- *Dépistage réactif*: Cette mesure permettait aux élèves qui obtenaient un résultat négatif un jour après l'identification d'un cas confirmé dans leur classe de continuer l'apprentissage en présentiel. Un deuxième test, réalisé 7 jours après l'identification, était recommandé. Si trois cas confirmés apparaissaient parmi les élèves de la même classe, la classe était fermée pendant sept jours. Les élèves qui ne se soumettaient pas au dépistage devaient rester en quarantaine pendant 10 jours.
- *Renforcement du dépistage réactif*: Cette mesure constituait une version améliorée du dépistage réactif, mise en œuvre en janvier 2022 pour faire face à l'augmentation du nombre d'infections chez les enfants causées par l'émergence du variant Omicron. Trois tests négatifs consécutifs au cours d'une semaine étaient requis pour les camarades d'un cas confirmé positif afin de continuer à fréquenter l'école. Les tests étaient effectués tous les 2 jours à partir du premier test réalisé lors de l'identification du premier cas. La période d'isolement pour les cas positifs durait 7 jours.

Au fur et à mesure de l'évolution de la pandémie, deux initiatives principales ont été menées pour surveiller le nombre de cas dans la population étudiante : i) une base de données nationale indiquant les taux d'incidence quotidiens et hebdomadaires, les taux de positivité et le pourcentage de personnes testées par rapport au nombre d'habitants, stratifié par groupe d'âge scolaire ; ii) la collecte de données de prévalence dans les écoles à des intervalles de temps spécifiques. Lors de la vague Alpha en 2021, des campagnes de dépistage ont été initiées dans les établissements scolaires des départements de l'Ain, de la Loire et du Rhône de la région Auvergne-Rhône-Alpes. Les dépistages étaient volontaires et faisaient partie des activités de surveillance dans les écoles maternelles, primaires, collèges et lycées. De plus, lors des vagues Delta et Omicron de l'automne 2021-2022, des campagnes de dépistage hebdomadaires ont été menées dans les écoles primaires des départements de l'Isère, du Puy-de-Dôme, du Rhône et de la Savoie de la même région en France.

Comme mesure de contrôle supplémentaire, la vaccination a été ouverte aux adolescents à partir du 15 juin 2021, tandis que les enfants ne sont devenus éligibles que le 22 décembre 2021 [7, 8].

Modélisation de la propagation de COVID-19 dans les établissements scolaire

Pour simuler la propagation de COVID-19 dans les établissements scolaires et étudier la dynamique dans les différentes phases, y compris l'émergence de la variante Alpha et Omicron BA.1, un modèle stochastique basé sur des agents à partir de réseaux d'écoles primaires et secondaires a été développé. Les réseaux d'écoles ont été construits sur la base de données réelles collectées avant la pandémie avec RFID sensors [9] et étendus dans le temps pour

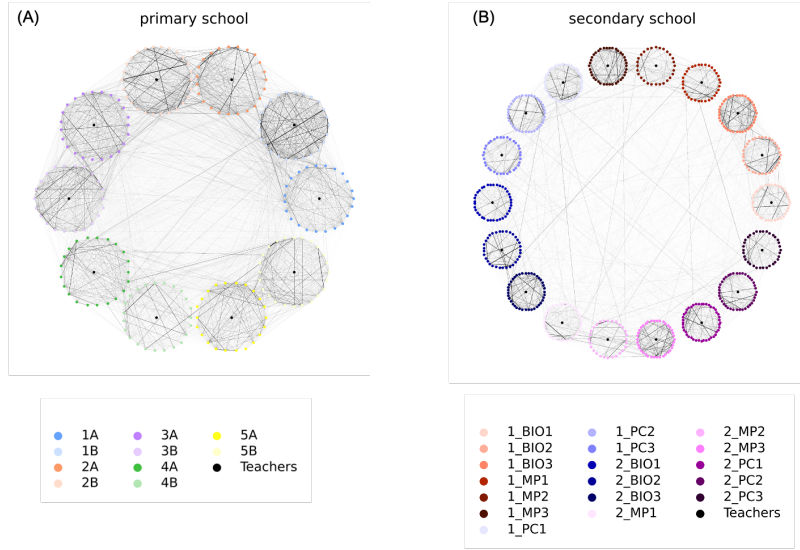


Figure 2: (A) L'ensemble des données sur l'école primaire comprend 232 élèves participants et 10 enseignants répartis dans 10 classes, avec une taille moyenne des classes de 23,2 élèves. (B) L'ensemble des données de l'école secondaire comprend 325 élèves participants issus de 9 classes, avec une taille moyenne de 35,8 élèves. Ces classes appartenaient à la deuxième année de classes préparatoires d'un lycée et étaient divisées en trois groupes en fonction de leurs spécialisations. Le réseau a ensuite été doublé pour inclure une année supplémentaire et des enseignants.

couvrir un intervalle de temps plus large. Les deux réseaux sont utilisés comme prototypes pour reproduire les contacts dans une école primaire et secondaire générique en France.

Chaque nœud du réseau suit la progression indiquée dans la Figure 3. Les individus susceptibles (S) peuvent devenir exposés (E) lorsqu'ils sont en contact avec une personne infectieuse. Tant qu'elles sont exposées, les personnes ne peuvent pas transmettre l'infection. Après une période de latence moyenne τ_E , ils entrent dans une phase prodromique (I_p) où ils peuvent propager la maladie sans présenter de symptômes. Ensuite, les individus peuvent soit rester asymptomatiques (I_{sc}) avec une probabilité de p_{sc} , soit développer des symptômes cliniques (I_c) avec une probabilité de $p_c = 1 - p_{sc}$. Les personnes qui se trouvent dans les compartiments prodromique et subclinique sont considérées comme moins infectieuses et passent souvent inaperçues à moins d'être testées [10–12]. Les personnes présentant des symptômes cliniques peuvent être identifiées avec une probabilité p_d et isolées pendant une période fixe Δq si elles sont testées positives grâce à des tests basés sur les symptômes. Si les enseignants doivent procéder à un isolement, ils sont temporairement remplacés par un individu sensible (S) jusqu'à ce que le test soit négatif ou pour une durée maximale de 2 semaines. Les probabilités p_{sc} et p_d dépendent de l'âge et sont généralement plus faibles pour les étudiants que pour les enseignants [12–18]. Après la phase infectieuse donnée par la somme des périodes prodromique et symptomatique (asymptomatique) $\tau_I = \tau_{I_p} + \tau_{I_{c/sc}}$, les individus entrent dans une phase transitoire (R_+) où ils ne sont plus infectieux mais peuvent encore être détectés comme positifs par des tests plus sensibles, tels que les tests PCR, en raison d'une présence virale résiduelle dans les voies respiratoires supérieures [19–21]. Enfin, les individus se déplacent vers le compartiment récupéré (R). Lorsque la variante Omicron est considérée, la réinfection est possible. Dans ce cas, les individus précédemment infectés par des variantes différentes d'Omicron peuvent contracter à nouveau l'infection (S^*) mais avec une probabilité réduite en

raison de la protection partielle fournie par l'infection naturelle [22, 23].

Les événements de transmission sont modélisés en tenant compte d'un double mécanisme. Tout d'abord, nous considérons les événements de transmission dus aux interactions au sein des écoles, à savoir les interactions entre les élèves et entre les élèves et les enseignants. Toutes ces interactions sont explicitement décrites dans le réseau scolaire spécifique. Cependant, les élèves et les enseignants sont également susceptibles de contracter le COVID-19 par le biais d'interactions qui ont lieu en dehors des locaux de l'école. Ce deuxième cas représente la circonstance dans laquelle le virus est introduit dans l'école à partir de la communauté. Par conséquent, nous incluons un certain nombre d'introductions au cours des simulations (cas générés en dehors du contexte scolaire) afin de simuler la manière dont elles contribuent à la propagation une fois qu'elles pénètrent dans l'école. La probabilité de transmission est proportionnelle au taux de transmission par contact et par unité de temps, à la susceptibilité en fonction de l'âge, à la transmissibilité en fonction de l'âge et du stade et à la durée du contact telle que rapportée dans le réseau.

Néanmoins, des événements de transmission peuvent également se produire en dehors du cadre scolaire, lorsque les enseignants et les élèves entrent en contact avec des membres de leur famille ou de la communauté. Pour modéliser ce type d'événement, nous envisageons un afflux hebdomadaire d'individus infectés de la communauté vers l'environnement scolaire. Pour ce faire, nous choisissons un pas de temps et un jour aléatoires en dehors des heures de cours et nous faisons passer certains individus des réseaux du statut sensible (S) au statut exposé (E). Le nombre hebdomadaire d'infections introduites à l'école est déduit de la prévalence communautaire dans des classes d'âge spécifiques (enfants, adolescents et adultes) [24] et tient compte de facteurs tels que la probabilité de détection et la taille de l'école [25, 26], comme nous l'expliquons ci-dessous. Nous avons utilisé comme source de données la plateforme GEODES de Santé publique France pour les incidences hebdomadaires par département et par âge. Nous distinguons deux cas principaux : 1. Cas importés (ou introduits) à la réouverture 2. Cas importés (ou introduits) pendant les sessions de cours. Lorsque les écoles sont fermées, les chaînes de transmission au sein de l'école sont interrompues. Par conséquent, à la réouverture de l'école, l'incidence communautaire compte exclusivement pour les introductions. Dans les semaines suivant la réouverture de l'école et pendant les sessions de cours, la prévalence communautaire représente une mesure combinée des infections introduites depuis l'extérieur de l'école et de celles qui se sont produites dans l'enceinte de l'école. Pour estimer le nombre attendu d'introductions au cours d'une semaine donnée, nous avons affiné le nombre d'introductions hebdomadaires, en le multipliant par un facteur afin d'actualiser la contribution des transmissions à l'intérieur de l'école.

Les caractéristiques spécifiques liées à l'âge, telles que la susceptibilité et la transmissibilité, ont été prises en compte. Nous avons également considéré que les individus pré-symptomatiques et asymptomatiques étaient moins infectieux que les individus symptomatiques [10, 12, 28–31]. En outre, nous avons considéré que les enfants ont une plus grande probabilité de développer des formes asymptomatiques et une probabilité réduite d'être identifiés comme des cas cliniques par rapport aux adultes [14–18, 32, 33]. Les séjours à chaque stade d'infection ont été déterminés à l'aide de distributions empiriques et adaptées au fil du temps en fonction des caractéristiques de la variante.

J'ai calibré le modèle aux données de prévalence recueillies sur le terrain en France pendant les vagues Alpha, Delta et Omicron. Celui-ci a permis d'estimer, par une approche de maximum de vraisemblance, le taux de transmissibilité par contact dans les écoles au cours de chaque phase. Les estimations ont fourni des indications sur le nombre de reproduction efficace spécifique à l'école et sur la contribution des écoles au nombre total d'infections chez les enfants. Afin d'identifier des stratégies sûres pour limiter la discontinuité et la transmission

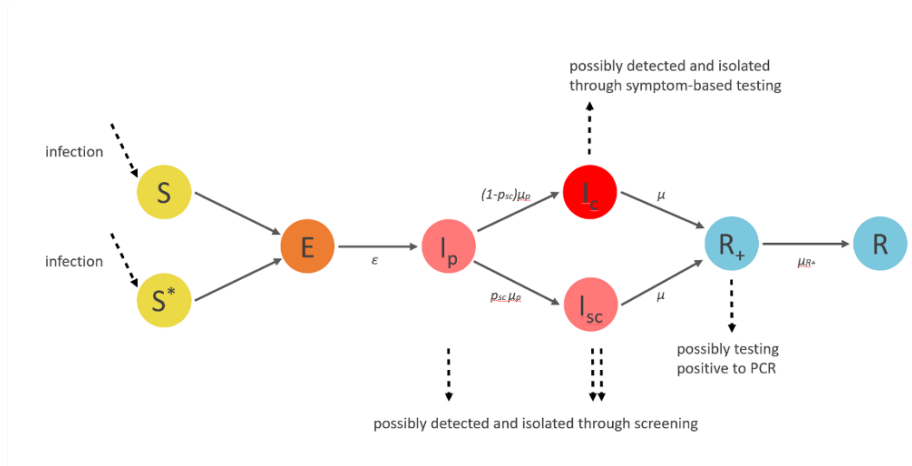


Figure 3: Schéma de la progression de la COVID-19 en l'absence de vaccination. S = susceptible ; E = exposé ; I_p = infectieux en phase prodromique ; I_s = infectieux asymptomatique ; I_c = infectieux symptomatique ; R_p = guéri mais détectable comme positif par des tests plus sensibles. ; R = guéri. Les lettres au-dessus des flèches indiquent le taux de transition entre les compartiments. Figure de l'article [27].

dans les écoles tout en optimisant les ressources, j'ai simulé un large éventail de stratégies de dépistage dans les écoles. Ces stratégies comprenaient le dépistage et l'isolement des personnes symptomatiques, le dépistage régulier et réactif des contacts étroits et les mesures de quarantaine comme celles adoptées en France. Le modèle a également intégré la vaccination afin d'évaluer son impact et fournir des indications utiles pour recommander la vaccination aux enfants de 5 à 11 ans en France. Pour évaluer l'efficacité, le nombre de cas, d'absences et de tests a été calculé et comparé afin d'évaluer les réductions associées.

Résultats et discussion

La pandémie de COVID-19 a eu un impact significatif sur la vie des enfants et des adolescents, perturbant leur routine quotidienne, leur éducation et leur bien-être général. Après la fermeture initiale, le gouvernement s'est attaché à trouver des moyens de maintenir les écoles ouvertes, reconnaissant leur rôle dans la promotion de l'apprentissage et du développement. Les questions de recherche explorées dans cette thèse ont donc été conçues pour trouver des stratégies qui pourraient permettre un apprentissage en personne en toute sécurité tout en améliorant notre compréhension de la transmission de COVID-19 dans les écoles.

Pour atteindre ces objectifs, j'ai développé un modèle stochastique basé sur des agents à partir de réseaux de contacts d'écoles primaires et secondaires afin d'étudier la dynamique de la transmission au cours de différentes phases de la pandémie, y compris l'émergence des variantes Alpha et Omicron BA.1. Les réseaux scolaires ont été construits sur la base de données réelles collectées avant la pandémie et étendus dans le temps pour couvrir un intervalle de temps plus large. En adaptant le modèle aux données de prévalence sur le terrain recueillies en France à différentes périodes, j'ai estimé le taux de transmission par contact dans les écoles au cours de chaque phase par une approche de maximum de vraisemblance. Les estimations ont fourni des indications sur le nombre de reproduction efficace spécifique à l'école et sur la contribution des écoles au nombre total d'infections chez les enfants. Afin d'identifier des stratégies sûres pour limiter la discontinuité scolaire et la transmission tout en optimisant les ressources, j'ai simulé un large éventail de protocoles scolaires. Ces stratégies comprenaient le dépistage et l'isolement des personnes symptomatiques, le dépistage régulier et réactif des

contacts étroits et les mesures de quarantaine. La plupart des stratégies simulées ont suivi celles appliquées en France et ont permis de mieux informer les autorités lors de la gestion de la crise COVID-19 [34–39]. Le modèle a également intégré la vaccination afin d’évaluer son impact sur les recommandations pour les enfants de 5 à 11 ans en France [40].

Nous avons montré que la transmission du virus SRAS-CoV-2 dans les écoles peut être influencée par divers facteurs, notamment les schémas de contact entre les élèves, l’incidence du virus dans la communauté, l’émergence de variantes et l’efficacité des mesures de contrôle. Les estimations du nombre de reproduction efficace spécifique à l’école (R_{school}) au cours de la vague Alpha en France ont montré que la transmission s’est produite à la fois dans les écoles primaires et secondaires, contrairement à ce qui avait été démontré précédemment, à savoir que les écoles ne constituaient pas un environnement à haut risque pour la transmission du SRAS-CoV-2 [41, 42]. Cette constatation souligne également la nécessité d’adopter des mesures plus strictes pour contrôler la transmission dans les écoles que la fermeture des classes après l’identification d’un cas. Anticipant la circulation de la variante Delta pour l’hiver 2021, j’ai identifié le dépistage hebdomadaire avec une adhésion élevée (supérieure à 75%) comme la meilleure stratégie pour réduire le nombre de cas et minimiser les jours de classe perdus. Nous avons montré que la force du dépistage régulier reposait sur l’identification précoce et l’isolement des individus susceptibles de propager le virus sans présenter de symptômes (formes pré-symptomatiques ou asymptomatiques). Ces résultats sont conformes aux études de modélisation antérieures [43, 44] et ont été confirmés ultérieurement par d’autres [45, 46], démontrant ainsi la solidité de l’efficacité du dépistage régulier. La nouveauté de notre étude réside dans l’intégration dans le modèle des estimations empiriques des niveaux de participation enregistrés tout au long des campagnes hebdomadaires pilotes et expérimentales. Les performances supérieures du dépistage hebdomadaire ont été préservées même lorsque des ressources d’essai et des conditions de forte incidence ont été prises en compte, comme lors de la vague Omicron au début de 2022. En particulier, nous avons montré que le dépistage réactif renforcé appliqué à l’échelle nationale en janvier 2022 en France impliquait une utilisation similaire des ressources de test par rapport à l’approche de dépistage hebdomadaire adoptée dans le canton de Bâle, en Suisse. Cependant, une augmentation imprévue de la demande de tests est causée par le dépistage réactif renforcé avec un contrôle très limité par rapport au dépistage hebdomadaire. Ce manque de prévisibilité dans l’approche du dépistage réactif a eu des effets en cascade sur les écoles et les familles, qui ont été minées par des demandes continues de tests et des discontinuités dans les activités scolaires.

À l’aide de scénarios, j’ai également évalué l’impact de la vaccination, révélant qu’elle pouvait fournir une protection collective significative à court terme si la couverture vaccinale était étendue. En revanche, lorsque la couverture était faible ou modérée, le dépistage régulier restait une stratégie importante pour détecter un nombre substantiel d’infections qui seraient passées inaperçues si la fermeture réactive des classes ou le dépistage réactif avaient été mis en place. Grâce à une expérience en conditions réelles, j’ai constaté que lors des variantes Delta et Omicron, plus transmissibles, les épisodes de transmission à l’intérieur des écoles représentaient environ la moitié des cas ou plus. En outre, en comparant les résultats du dépistage expérimental et de la stratégie nationale, j’ai pu confirmer les données de modélisation antérieures concernant l’efficacité du dépistage hebdomadaire dans la prévention de la transmission à l’école par rapport au dépistage réactif.

Au cours de la pandémie de COVID-19, la circulation des maladies respiratoires, y compris la grippe et le virus respiratoire syncytial (VRS), a diminué dans de nombreux pays [47–49]. Au cours de la saison 2022-2023, l’activité du virus de la grippe est revenue à des niveaux presque prépandémiques dans les pays européens, avec un début plus précoce et des pics de positivité plus élevés que lors des quatre saisons précédentes [50]. De même, les taux de transmission du VRS ont augmenté et la saison a commencé plus tôt que d’habitude [51].

Récemment, l'Australie a connu une saison grippale précoce en juin 2023, les enfants étant particulièrement touchés par rapport aux autres groupes d'âge [52]. La diminution des cas de grippe et de VRS observée au cours des premières phases de la pandémie de COVID-19 peut être largement attribuée aux mesures strictes de santé publique mises en œuvre, notamment le port obligatoire de masques, l'éloignement physique, les couvre-feux et les restrictions sur les rassemblements. Ces mesures ont non seulement permis de réduire efficacement le nombre de cas de COVID-19, mais ont également eu un impact positif sur le contrôle de la transmission d'autres maladies respiratoires, telles que la grippe et le VRS [49, 53]. D'autre part, ce déclin de la circulation de la grippe et du VRS pendant la pandémie a également entraîné une sorte de "dette d'immunité" [53]. L'exposition réduite à ces virus a entraîné un manque d'immunité naturelle, créant un vaste réservoir de personnes sensibles lorsque les mesures strictes ont été assouplies. En conséquence, on a observé une modification des schémas saisonniers et une augmentation notable des cas de grippe et de VRS. En hiver, nous nous attendons à une co-circulation du SRAS-CoV-2, de la grippe, du VRS et d'autres virus respiratoires, affectant particulièrement les enfants. Cette situation peut être plus difficile si les vaccins pour certains virus, comme le VRS, ne sont pas encore officiellement disponibles, ou si la couverture vaccinale des enfants reste faible ou diminue avec le temps, comme on l'a vu avec le COVID-19.

Dans ce contexte, il est important de comprendre la dynamique de transmission de ces virus dans les écoles. Les écoles représentent des lieux densément peuplés où les gouttelettes respiratoires et la dispersion des aérosols peuvent être des modes de transmission dominants en l'absence de mesures de prévention et de contrôle. Dans ce dernier cas, de petites particules contenant le virus peuvent en effet rester en suspension dans l'air et être inhalées par d'autres élèves dans la même salle, ce qui représente une voie de transmission supplémentaire en plus des contacts de proximité. Ainsi, l'étude de la propagation de la grippe, du VRS ou des deux dans de tels environnements nous permettrait d'évaluer la charge des virus respiratoires chez les enfants, d'identifier des schémas et de concevoir des stratégies d'atténuation efficaces. Le modèle à base d'agents que j'ai développé est bien adapté à la caractérisation de la transmission en milieu scolaire. Il peut donc être adapté pour étudier la transmission de la grippe, du VRS ou des deux dans les années suivant la pandémie de COVID-19.

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SORBONNE UNIVERSITÉ

DOCTORAL THESIS

Modelling COVID-19 spread in educational settings for safe in-person learning

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Abstract

Modelling COVID-19 spread in educational settings for safe in-person learning

When COVID-19 emerged as a global pandemic in March 2020, schools were among the first settings to be closed to curb the transmission of SARS-CoV-2. However, the choice of closing school for a relatively long time was quite controversial and largely debated, especially for the harmful effects on students' well-being and learning development. Therefore, governments worldwide gradually reintroduced in-person activities in schools, implementing various control measures to manage positive cases. The approaches taken by different countries varied, with some adopting reactive strategies in response to confirmed cases, while others implemented more proactive measures as the pandemic progressed. Schools remained vulnerable environments, especially in the absence of vaccination for younger students and the emergence of more contagious variants such as Delta and Omicron. In this thesis, I estimated the transmissibility of SARS-CoV-2 within schools for different variants and evaluated a range of testing and screening strategies to provide safe options for keeping schools open while minimizing educational disruption.

To achieve this aim, I developed an agent-based model to simulate SARS-CoV-2 spread through face-to-face interactions among students and teachers in a primary and secondary school in France under different epidemic contexts. I fitted the model to the student prevalence data gathered from pilot and experimental screening campaigns conducted in specific pandemic phases, from the emergence of the Alpha variant in 2021 to the Omicron variant in early 2022 in France. I thus estimated the effective reproductive number in both schools and the contribution of school-based transmission to the overall spread in children. I then assessed the effectiveness of different intervention protocols in limiting importation and onward transmission, reducing school absence, and optimizing testing resources through a cost-benefit analysis.

The results contained in this dissertation shed light on the role of school contacts as a potential source of renewed transmission during the COVID-19 pandemic, showing that transmission in schools represented a considerable contribution. According to our results, regular screening with large enough adherence can reduce cases and absences even under high-incidence conditions, as experienced during the Omicron wave of early 2022. The higher effectiveness achieved by weekly screening compared to reactive strategies is also confirmed by our retrospective analysis of a real-world experiment in a selected number of French primary schools during the Delta and Omicron waves between the end of 2021 and the beginning of 2022.

Although COVID-19 no longer represents a global emergency, it will continue to circulate with other seasonal respiratory viruses (i.e., influenza, Respiratory Syncytial Virus, etc.) in children during the winter. The modelling framework developed in this thesis is well-suited for studying the transmission of respiratory viruses in densely populated settings, such as schools, quantifying the extent, and evaluating the impact of potential mitigation measures in the future.

Résumé

Modélisation de la propagation de COVID-19 dans les établissements scolaires afin de maintenir l'apprentissage en personne en toute sécurité

Lorsque le COVID-19 est apparu comme une pandémie mondiale en mars 2020, les établissements scolaires ont été parmi les premiers lieux à être fermés pour freiner la transmission du SRAS-CoV-2. Cependant, le choix de fermer les écoles pendant une période relativement longue a été très controversé et largement débattu, notamment en raison des effets néfastes sur le bien-être des élèves et le développement de l'apprentissage. C'est pourquoi les gouvernements du monde entier ont progressivement réintroduit les activités en personne dans les écoles, en mettant en œuvre diverses mesures de contrôle pour gérer les cas positifs. Les approches adoptées par les différents pays ont varié, certains adoptant des stratégies réactives en réponse aux cas confirmés, tandis que d'autres ont mis en œuvre des mesures plus proactives au fur et à mesure que la pandémie progressait. Les établissements scolaires sont restés des environnements vulnérables, en particulier en l'absence de vaccination des jeunes élèves et en raison de l'émergence des variantes plus contagieuses telles que Delta et Omicron. Dans cette thèse, j'ai estimé la transmissibilité du SRAS-CoV-2 dans les établissements scolaires pour différents variants et j'ai évalué une série de stratégies de test et de dépistage afin de fournir des options sûres pour maintenir les écoles ouvertes tout en minimisant les suspensions de l'enseignement.

Pour atteindre cet objectif, j'ai développé un modèle individus-centrés afin de simuler la propagation du SRAS-CoV-2 par le biais d'interactions en face à face entre les élèves et les enseignants d'une école primaire et secondaire en France dans différents contextes épidémiques. J'ai adapté le modèle aux données de prévalence des élèves recueillies lors de campagnes de dépistage pilotes et expérimentales menées lors de phases pandémiques spécifiques, depuis l'émergence de la variant Alpha en 2021 jusqu'à la variant Omicron au début de 2022 en France. J'ai ainsi estimé le nombre de reproducteurs effectifs dans les deux établissements scolaires et la contribution de la transmission en milieu scolaire à la propagation chez les enfants. J'ai ensuite évalué l'efficacité de différents protocoles d'intervention pour limiter l'importation et la transmission ultérieure, réduire l'absentéisme scolaire et optimiser les ressources de dépistage par le biais d'une analyse coût-bénéfice.

Les résultats de cette thèse mettent en lumière le rôle des contacts scolaires en tant que source potentielle de renouvellement de la transmission pendant la pandémie de COVID-19, en montrant que la transmission dans les établissements scolaires a représenté une contribution considérable. D'après nos résultats, un dépistage régulier avec une adhésion suffisante peut réduire le nombre de cas et d'absences même dans des conditions d'incidence élevée, comme cela a été le cas lors de la vague Omicron au début de 2022. L'efficacité supérieure du dépistage hebdomadaire par rapport aux stratégies réactives est également confirmée par notre analyse rétrospective d'une expérience en conditions réelles dans un certain nombre d'écoles primaires françaises pendant les vagues Delta et Omicron entre la fin de 2021 et le début de 2022.

Bien que le COVID-19 ne représente plus une urgence mondiale, il continuera à circuler avec d'autres virus respiratoires saisonniers (grippe, virus respiratoire syncytial, etc.) chez les enfants pendant l'hiver. Le cadre de modélisation développé dans cette thèse est adapté à l'étude de la transmission des virus respiratoires dans des environnements densément peuplés tels que les écoles, à la quantification de leur portée et à l'évaluation de l'impact d'éventuelles mesures de mitigation.

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Introduction

Schools are environments where a large number of students engage in close and prolonged interactions within closed spaces. By their nature, schools can create favourable conditions for the transmission of respiratory viruses. Young children can in fact play a key role in spreading the infection through school contacts, which in turn may affect their parents, thereby increasing the overall transmission levels in the community. This was the case of the 2009 H1N1 influenza pandemic, where transmission at the population level was substantially lower when schools were closed during holidays and higher when schools were back in session [1, 2, 3, 4]. For this reason, schools were one of the first settings to be shut down in response to the explosion of cases around the world in March 2020 [5]. Once they reopened, the limited knowledge about the SARS-CoV-2 circulation in children and adolescents made it difficult to preemptively identify the intervention necessary that would conciliate in-person learning with pandemic control. This coupled with the evolving landscape of the pandemic, including the emergence of new variants, continued to pose challenges to the selection of effective strategies and the management of normal school life.

Since the start of the COVID-19 pandemic, mathematical modelling offered projections for the course of the pandemic and the impact of measures such as lockdowns, curfews, and social distancing, but a hazy understanding was still persistent regarding the transmission among students. This dissertation aims to shed light on the role of COVID-19 school transmission for informing and refining control strategies in educational settings during the Alpha, Delta, and Omicron waves. By developing an agent-based model over empirical school networks, I provide alternative strategies to school closures to contrast viral spreading and educational disruption. Field screening data are used to fit the model and reproduce specific student prevalence conditions. In such a way, I have been able to enhance the ability of authorities to effectively manage COVID-19 in schools and reduce its impact on children. The work presented in this dissertation is organized into five Chapters.

In Chapter 1, I introduce the initial evidence regarding the characteristics of COVID-19 in children and adolescents, along with an overview of the main recommendations, focusing specifically on French school protocols.

Chapter 2 describes the three datasets containing information on student prevalence collected during different pandemic phases in France used to fit the model. Then, the construction of the synthetic networks derived from empirical contact data is introduced. Finally, the transmission model and the inference framework for estimating the transmission rate at school are presented.

Chapter 3 presents the results of my first published work [6] and provides estimates of the school-specific effective reproductive number during the Alpha wave in Spring 2021.

Chapter 3 also contains the results of a cost-effectiveness analysis of school protocols in a Delta scenario for the following academic year, 2021-2022.

Chapter 4 focuses on my second published work and refers to the Omicron phase [7], which was characterized by high incidence levels in children. In this Chapter, I take the school protocols implemented in France, Italy, and Basel Canton in Switzerland as case studies and I analyze the response of each strategy in terms of testing resources, case prevention, and school absences around the peak.

In Chapter 5, I present an ongoing work involving a retrospective analysis of school contribution in primary school children during the Delta and Omicron waves and a weekly screening regimen trialled in a set of French primary schools.

The final part of this dissertation contains a summary of the results and a discussion of their reliability, hypotheses, limitations, and potential directions for future research.

The stochastic agent-based model was implemented in **C** language while data analysis, data pre- and post-processing, and plots were performed in **Python**.

Publications included in this thesis

[6] Colosi, E., Bassignana, G., Contreras, D. A., et al. Screening and vaccination against COVID-19 to minimise school closure: a modelling study. *The Lancet Infectious Diseases* 22, 977–989. (2022)

[7] Colosi, E., Bassignana, G., Barrat, A., et al. Minimising school disruption under high incidence conditions due to the Omicron variant in France, Switzerland, and Italy, in January 2022. *Eurosurveillance* 28, 2200192. (2023)

Technical Reports

The research findings contained in this dissertation were promptly communicated to French authorities over the course of the academic year 2021 and in preparation for the new one. Here is a list of contributions ended in technical reports.

[8] Avis Conseil Scientifique, *Autotest: une opportunité pour la santé publique* (April 2021)

[9] HAS, *Évaluation de l'intérêt des tests antigéniques rapides sur prélèvement nasal pour la détection du virus SARS-CoV-2 (Méta-analyse)* (April 2021)

[10] Report, *Étude sur les conditions de mise en oeuvre d'une stratégie de sortie de la pandémie de SARS-CoV-2* (June 2021)

[11] Avis Conseil Scientifique, *Reagir maintenant pour limiter une nouvelle vague associée au variant Delta* (July 2021)

[12] Avis Conseil Scientifique, *Fin de la période estivale et pass sanitaire Rentrée de septembre 2021* (August 2021)

[13] Avis Conseil Scientifique, *Enjeux de la rentrée scolaire* (September 2021)

[14] HAS, *Stratégie de vaccination contre la Covid-19* (December 2021)

Other publications linked to this thesis

- [15] Colosi, E., Bassignana, G., Barrat, A. and Colizza, V. Modelling COVID-19 in school settings to evaluate prevention and control protocols. *Anaesthesia Critical Care & Pain Medicine* 41, 2, 101047 (2022)
- [16] Contreras, D.A., Colosi, E., Bassignana, G., et al. Impact of contact data resolution on the evaluation of interventions in mathematical models of infectious diseases. *Journal of The Royal Society Interface* 19, 191, 20220164 (2022)

COVID-19 in children and adolescents: evidence and school protocols

In this Chapter, I will briefly present the evidence available on SARS-CoV-2 transmission and COVID-19 disease in children and adolescents at the early stage of the COVID-19 pandemic. First, I will discuss the choice of closing schools during a pandemic, pointing out the benefits as well as the social and economic implications that had already emerged during the pandemic of H1N1 in 2009. Second, I will present the most common school interventions adopted in Europe in the absence of vaccination coverage, with a focus on France. Finally, I will illustrate the surveillance data used in the following Chapters for my research.

1.1 Early evidence and first recommendations

1.1.1 COVID-19 in children and adolescents

COVID-19 is a respiratory illness caused by SARS-CoV-2, initially identified in China in December 2019 [17] and declared a pandemic by the World Health Organization (WHO) in March 2020. Transmission of the virus occurs mainly through inhalation of respiratory fluids (droplets or aerosols) from infected individuals when they engage in activities such as talking, sneezing, coughing, or singing. Exposure to infectious particles can happen during face-to-face contact or by sharing the same room with an infected individual. In cases of scarce ventilation, aerosol particles produced by an infected person can remain suspended in the air from a few minutes to hours, increasing the viral concentration in the air and thus the risk of exposure for the individuals in the same room. Less frequently, transmission can occur by touching surfaces or objects which have been contaminated by the virus (fomite-mediated transmission) [18].

Clinical manifestations range from asymptomatic to severe respiratory distress, with children and adolescents typically experiencing milder symptoms compared to adults [19]. Symptoms in children and adolescents can include fever, cough, sore throat, and, less frequently, diarrhoea and vomiting [20]. Severe forms are rare in these age classes, with a low risk of hospitalisation and death [21, 22].

Regarding the susceptibility of children and adolescents to infection, initial evidence mainly suggested a lower susceptibility compared to adults. The study by Zhang et al. [23]

was one of the first studies to infer the relation between age profile and susceptibility to infection. By using a statistical regression model and contact tracing data gathered between January and March 2020 in China, where the outbreak first exploded, they assessed how age, together with other covariates (gender, type of contact, etc.), could impact the risk of infection. They found that children aged 0–14 years had lower susceptibility to SARS-CoV-2 infection than adults between 15 and 64 years of age, with an odds ratio of 0.34. This result aligned with the findings from a different type of study, based on fitting an age-stratified transmission model to the reported case distributions in the early phase of the epidemic in China (8 December 2019 to 1 February 2020) [24]. According to the estimates provided in the study, individuals aged under 20 years were 50% less susceptible to SARS-CoV-2 infection compared to those aged over 20 years. Additionally, in the early phase, different countries reported lower seroprevalence values in children than in adult groups. For instance, in a serological study conducted in Geneva, it was observed that young children between the ages of 5 and 9 years had a lower risk of contracting the infection compared to those aged 20 to 49 years [25]. Similarly, a serological survey conducted in Spain between April and May 2020 also found lower infection rates in children [26]. These lower infection rates in children could potentially suggest reduced susceptibility to the virus. In contrast to these findings, a contact tracing study conducted in China found that children were at a similar risk of infection as the general population [27]. The presence of mixed results in the first year of the pandemic made it difficult to obtain a clear picture of the susceptibility of children and adolescents to the virus. The understanding was additionally complicated by potential sources of bias, such as altered contact patterns during school closures and, consequently, altered risk of exposure in children. Schools were largely closed in the periods considered in the studies cited before as part of large-scale interventions, so the lower susceptibility could have resulted from the reduced opportunity to have contact. Selective symptom-based testing and under-detection may have also played a role in estimating the true incidence in children, affecting the susceptibility estimates if adjustments were not applied to correct them. For these reasons, susceptibility remained widely debated throughout the pandemic and subject to revision from the emergence of the Alpha variant onward [28].

Another much-discussed topic was whether children and adolescents were intrinsically less infectious than adults. At the beginning, although limited evidence on age differences in transmissibility was available in the literature, indications suggested that transmissibility could somewhat increase with age [29, 30]. As a consequence, the transmission risk from children to other children or adults seemed to be lower than that from adults to children. Adolescents appeared instead to be more similar to adults. Also in this case, infectiousness estimates may have been affected by errors and biases. In particular, the correct identification of an index case in contact tracing studies and the number of secondary cases generated may have been hampered by asymptomatic forms in children. The alteration of contact rates during school closures may have been a further obstacle to the correct quantification.

Other possible determinants of the disease transmission risk were the viral shedding kinetics, duration, and linkage with infectiousness. Early in the pandemic, a preprint analyzing viral loads observed during routine screening testing in Berlin between January and

May 2020 suggested that children shed similarly to adults [31]. This preliminary result was in line with the findings of another study that examined the number of RNA copies from nasopharyngeal swabs in symptomatic children [32]. However, these results did not necessarily mean that children were as infectious as adults. The relationship between viral load and infectiousness is complex, since other factors, such as the host immune response and disease progression, might also influence the infectiousness. Furthermore, viral load values and duration might also vary depending on the sampling sites. For example, findings indicated that the viral load in children could persist longer in the gastrointestinal tract than in the respiratory tract [33]. Finally, according to a systematic review and meta-analysis that collected studies published until June 2020, the average shedding duration of SARS-CoV-2 was positively associated with age [34].

In conclusion, almost a year after the start of the pandemic, a lot of uncertainties still surrounded key epidemiological parameters. The conflicting results within these parameters, the absence of experiences with schools fully open, the lack of testing in children, and the asymptomatic forms prevented an understanding of SARS-CoV-2 transmission in children and adolescents in educational settings, making it difficult to define strategies *a priori* to manage the school reopening. In this situation, the relationship between school contacts and COVID-19 transmission quickly became an urgent question. In this thesis, I will use mathematical modelling to address gaps in school transmission and support the design and implementation of effective school interventions.

1.1.2 School closure

Following the declaration that COVID-19 had become a global pandemic in early March 2020, many governments in Europe decided to close schools of all levels as a first attempt to slow down the viral circulation (Figure 1.1). This decision was based on the experience gained in the context of the 2009 influenza H1N1 pandemic, for which the impact of school closures and the role of children in the spread were extensively studied. During the H1N1 pandemic, children were shown to be more susceptible to infection and had a larger attack rate compared to adults [1, 35]. Consequently, by closing schools, potential risk contacts could be prevented, and the likelihood of transmission and carrying infection beyond school premises could be reduced. For instance, holiday breaks were shown to help flatten the H1N1 epidemic curve in the UK as a result of reduced contact mixing [36]. Conversely, school reopening during the H1N1 pandemic was found to be associated with a rebound in cases in England [37] and a wider community incidence rate in the US [2].

Similar findings on reduced transmission in correspondence with school holidays or closures and the reverse effect were also observed in the context of seasonal influenza. In Israel, a significant reduction in respiratory infections occurred after the school closures due to a two-week teachers' strike [38]. According to a study examining ILI (influenza-like illness) rates spanning from 1985 to 2006 in France, school holidays could prevent 16% – 18% of seasonal influenza cases [39]. This was in line with another quantitative study analyzing the school closures in Arizona between the school years 2004 and 2008. The analysis showed that school closures might prevent or delay up to 42% of potential influenza cases among

school-aged children. In addition, during the school closure periods, the ratio of illness in school-aged children significantly decreased compared to that of adults and non-school-aged children [40].

The closure of schools was therefore proposed in the pandemic preparedness plans following the 2009 pandemic as a mitigation measure to limit the spread, especially if applied at the early stage [41]. However, although school closures proved to be effective and were somewhat encouraged, SARS-CoV-2 and pandemic influenza had critical distinctions. Since the beginning of the pandemic influenza, children consistently exhibited higher infection rates, while results showed their heightened susceptibility to infection compared to adults [1, 2, 3, 4]. Moreover, disease severity was stronger in children than adults, which further justified school closures. In contrast, COVID-19 showed a steep age gradient, with children at a lower risk of developing severe symptoms and more likely to remain asymptomatic. The limited testing in children also resulted in a smaller number of reported cases in the paediatric population compared to other age groups. Secondly, school closures due to influenza usually ranged from 1 day to 2 weeks and coincided mainly with holidays, whereas COVID-19 caused an average loss of 9 weeks just between April and August 2020 in Europe [42]. To ensure learning continuity, different alternatives were implemented in the meantime, such as e-learning platforms facilitating teacher and pupil interaction, national television programmes, or lessons on social media platforms [43]. Despite this, digital learning could not be considered a substitute or sustainable in the long term. According to the 2nd survey by UNESCO, UNICEF, World Bank, and the OECD, online learning was perceived globally as very effective only in 36% of cases, followed by TV (28%), take-home materials (23%) and, radio (20%) [44]. Furthermore, in the context of the influenza pandemic, some studies already questioned the negative consequences associated with school closures [45, 46, 47]. The potential risks associated with school closure included detrimental effects on mental health, a loss of important social interactions, decreased educational achievements, and reduced productivity. These considerations on the benefits and drawbacks associated with school closures also extended to the COVID-19 pandemic. As reported by UNICEF [48], the consequences associated with school closure during the COVID-19 could have long-lasting effects extending over several years. Early estimates in the pandemic indicated that more than 100 million children worldwide would fall below the minimum proficiency level in reading due to school closures caused by the COVID-19 pandemic [49]. Additionally, school closures restricted access to vital resources like food and healthcare services and exacerbated the issue of digital poverty among disadvantaged students. Finally, as previously observed during the 2009 pandemic [47], school closures also had an economic impact on parents who were forced to take time off from work to care for their children.

Hence, despite the fact that no evidence was yet available regarding the extent of transmission within schools due to their overall closure, there was general advocacy for school reopening with mitigation measures in place [44, 50]. The objective of this dissertation is to assess the transmission of COVID-19 within school settings and evaluate the most effective protocols for allowing schools to remain safely open while minimizing disruptions to education during the Alpha, Delta, and Omicron waves.

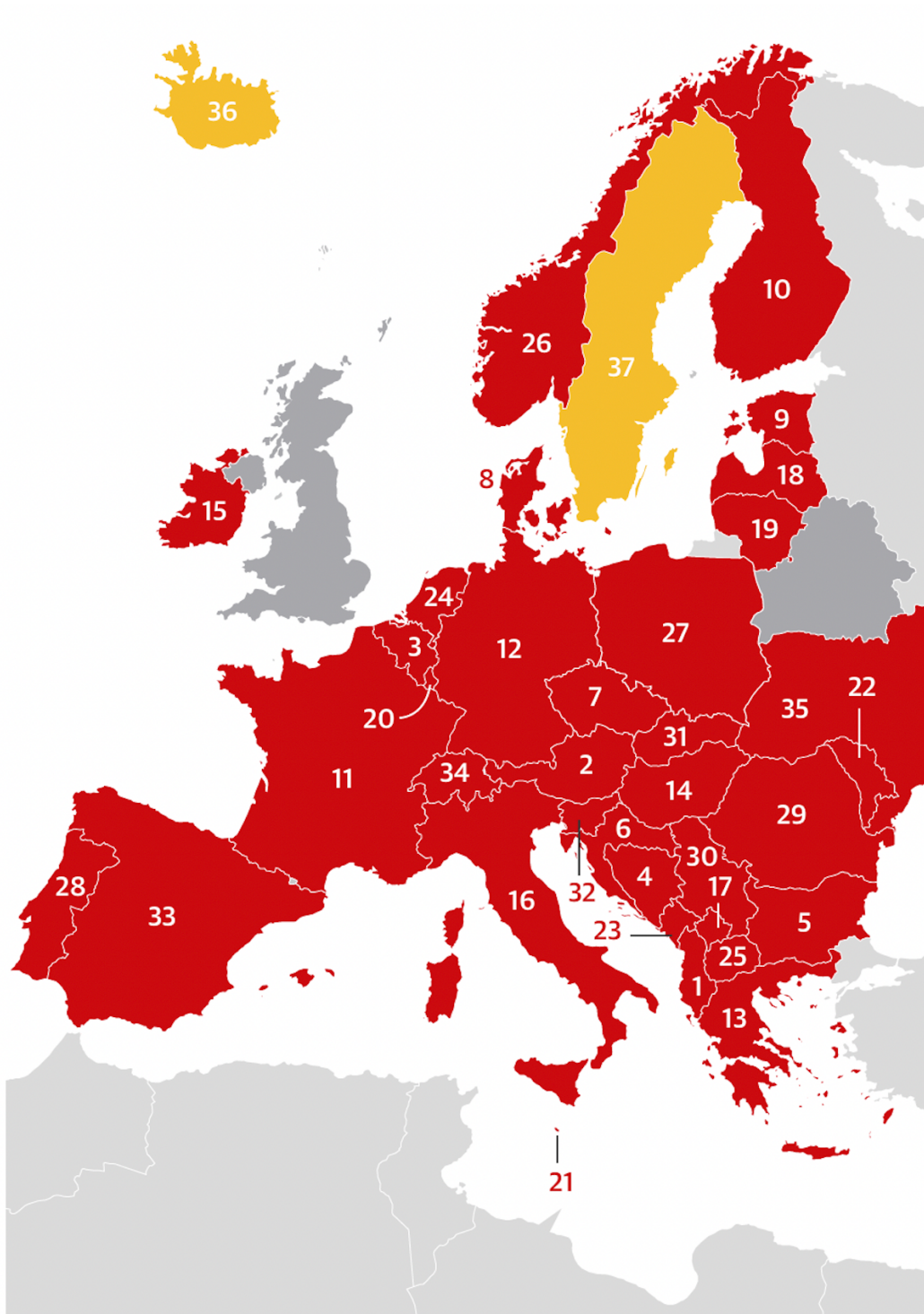


FIGURE 1.1: In red countries which adopted full closure (Albania, Austria, Belgium, Bosnia and Herzegov., Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kosovo, Latvia, Lithuania, Luxembourg, Malta, Moldova, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Switzerland, Ukraine), in yellow countries which adopted partial closure (Iceland, Sweden).

Source: The Guardian, *How do coronavirus containment measures vary across Europe?*, [51]

1.2 From closure to reopening: measures at school

1.2.1 School protocols in Europe

After the shutdown in April 2020, schools started partially reopening across Europe. Experiences with school reopening varied across countries according to national policies and public health guidance. However, some common measures were implemented in many European countries to reduce the risk of transmission in schools. The measures applied at schools can be broadly categorized as follows:

- Physical distancing measures to reduce the opportunity to make contacts
- Hygiene and safety measures to make contacts safer
- Testing measures and subsequent actions

According to the ECDC report [52], the most commonly recommended physical distancing measures were: ensuring physical distance (i.e., separating tables in the classroom), staggered arrival times in educational facilities and, cancellation of indoor activities (Figure 1.2, left). Mostly promoted hygiene and safety measures were instead: staying home when sick, promoting hand hygiene and respiratory etiquette, and regular ventilation of classrooms (Figure 1.2, right). In terms of testing and screening strategies, some differences in the extent to which they were enforced emerge across countries. Only a few countries implemented regular testing protocols early on in the pandemic or made it mandatory (UK [53], Switzerland [54], Austria [55]), while the majority applied testing of symptomatic individuals or of those who have been in close contact with a confirmed case. Around 82% of responding countries to the survey launched by the ECDC recommended that schools carried out contact tracing of positive cases linked to educational settings in collaboration with public health authorities. Most of the time, contact tracing was translated in class or school closure following the identification of a first symptomatic case, especially at the reopening after the shutdown. This was the case of Italy [56] and Germany [57]. However, school protocols have constantly evolved over the course of COVID-19, based on the local epidemiological situation and public health guidance. For instance, Germany introduced a mandatory self-test for students and teachers in April 2021 after the Easter break [58]. Danish authorities instead introduced a reactive screening system in schools in September 2021 as a substitute for class closure when a contact case was identified. This approach involved providing rapid tests to students who had been in contact with a positive case, to be taken at school as soon as possible and on days 4 and 7 after the potential exposure [59]. Starting in November 2021, the Danish protocol in schools was adjusted to include weekly screenings [60]. School protocols in France also varied over time. The school protocols adopted in France will be illustrated in the next Subsection (Subsection 1.2.2).

1.2.2 School protocols in France

Primary and secondary schools were closed during the first lockdown in France, from 17 March to 10 May 2020 [61]. Since 11 May 2020, schools gradually reopened in France under

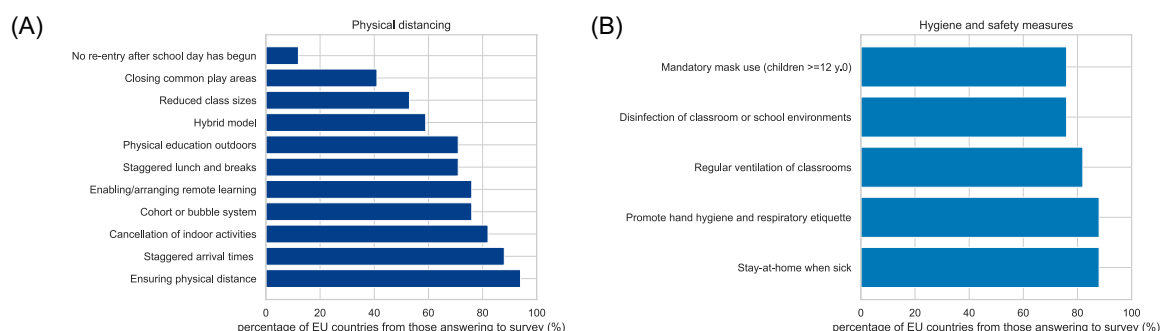


FIGURE 1.2: (A) Percentage of European countries that adopted one of the following physical distancing measure: ensuring physical distance, staggered arrival times, cancellation of indoor activities, cohort or bubble system, enabling/arranging remote learning, staggered lunch and breaks, physical education outdoors, hybrid model, reduced class sizes, closing common play areas, no re-entry after the school day has begun. (B) Percentage of European countries who adopted one of the following sanitary measures: stay-at-home when sick, promoting hand hygiene and respiratory etiquette, regular ventilation of classrooms, disinfection of classroom or school environments, mandatory mask use. The mean and median number of school mitigation measures was 13 (IQR 11-16). Seventeen countries responded to the surveys: Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Finland, Greece, Ireland, Latvia, Liechtenstein, Netherlands, Romania, Slovenia, Spain, and Sweden. Source: ECDC report 'COVID-19 in children and the role of school settings in transmission - first update' [52]

the health protocols of the High Council for Public Health (HCSP) [62]. For the academic year 2020-2021, the main principle was promoting in-person lessons for all pupils at all levels and throughout the school year to ensure the students' well-being while limiting the circulation of the virus [63]. In the event of a class or school closure, the educational continuity plan (online courses, virtual classes, etc.) was applied. This principle was kept throughout the pandemic.

Physical distancing and sanitary measures

At the end of the first lockdown, the recommendations provided by the health authorities for primary and secondary schools in terms of physical distancing consisted in keeping a one-meter distance between the teacher and pupils and between pupils when they were side by side or face to face in closed spaces (including the classroom). Physical distance could not apply in outdoor spaces between pupils of the same class or group, including sports activities. However, it had to be maintained in all cases between pupils of different groups (classes, class groups, or levels). For the school year 2020-2021, wearing a face mask became mandatory for students of secondary schools and extended also to primary students in October 2020. In January 2021, indoor physical activities were suspended and canteens were reorganized to limit the mixing of students. Distance learning was activated in April 2021 in anticipation of school holidays common to all French zones. The application of barrier gestures such as frequent hand washing, coughing or sneezing by covering the mouth with the elbow, or avoiding handshakes was encouraged. Ventilation of classrooms every 3 hours for 15 minutes as cleaning and disinfection of premises and equipment were incentivized as well. All these measures were framed in a more organized tiered system for the school year

2021-2022. Each level was triggered by a specific epidemic context. Moving from one level to another could lead to switching to hybrid learning for secondary students or stricter rules to avoid mixing and face-wearing. Figure 1.3 shows a schematic representation of the guidelines provided by the French Ministry of Education in terms of sanitary protocols, in-person learning, and regulation of sports activities for the school year 2021-2022.

	Level 1	Level 2	Level 3	Level 4
Schooling system	In person lessons for primary, middle and high school	In person lessons for primary, middle and high school	In person lessons for primary and middle school Hybrid learning in high school	In person lessons for primary school Hybrid learning in middle and high school (50% in-person lessons, 50% in remote lessons)
Sanitary protocol	Air ventilation and hand washing Mask wearing in indoors spaces from middle school, staff included No big gatherings Disinfection of surfaces 1 per day	Air ventilation and hand washing Mandatory mask wearing in indoor spaces from primary school, staff included Limited mixing among students of the same grade Disinfection of surfaces more than 1 time per day	Air ventilation and hand washing Mandatory mask wearing in indoor and outdoor spaces from primary school, staff included Limited mixing among students of the same grade. Limited mixing for primary students with classmates during canteen Frequent disinfection of tables and surfaces per day	Air ventilation and hand washing Mandatory mask wearing in indoor and outdoor spaces from primary school, staff included Limited mixing among students of the same grade. Limited mixing for primary students with classmates during canteen Frequent disinfection of tables and surfaces per day
Sport activities	No restrictions	No restrictions on outdoor spaces. In indoor spaces, only activities without contacts	Activities compatible with the measures on face mask wearing and physical distancing	Only outdoor activities with an intra-personal distance of 2 meter

FIGURE 1.3: Physical distancing and sanitary measures for the school year 2021-2022, released on September 2021 by the Ministry of Education [64]

Contact tracing and screening

At the start of the school year 2020-2021 in September 2020, contact tracing was deployed as an additional control measure to limit the SARS-CoV-2 circulation. This measure was also kept for the school year 2021-2022 with some modifications [65] (see section *Protocols evolution*). Throughout these two school years, the most adopted contact tracing strategies were:

- *Reactive class closure*. This measure was implemented for the first time at the beginning of the school year in September 2020 and iterated with some modifications until December 2021. Initially, this measure implied the closure of the class after the identification of 1 confirmed positive case and the closure of the school after 3 confirmed positive cases in the same class. The threshold for closing a class varied over time. It was raised to 3 cases in the same class at the end of September 2020 and then lowered again to 1 case with the arrival of the Alpha variant in February 2021. Isolation of confirmed cases and class closure lasted 7 days.

- *Reactive screening.* This measure was initially tested in primary schools across 10 French departments between October and November 2021 [66]. It was then implemented nationwide in December 2021, just two weeks before the Christmas holidays. This measure enabled students who tested negative one day after the identification of a confirmed case in their class to continue with classroom learning. A second test after 7 days from identification was recommended. If three confirmed cases appeared among pupils in the same class, the class was closed for seven days. Pupils who did not comply with the screening had to stay in quarantine for 10 days.
- *Strengthened reactive screening.* An enhanced version of the reactive screening was implemented in January 2022 to address the rising number of infections in children caused by the emergence of the Omicron variant. Three consecutive negative tests within a week were required for the classmates of a confirmed positive case in order to continue attending school. The tests were conducted every 2 days starting from the initial test administered upon the identification of the first case. The isolation period for positive cases lasted for 7 days.

As vaccination became available for adolescents in May 2021 [67], contact tracing strategies varied slightly in secondary schools. Class closure was no longer implemented. A distinction was made between vaccinated and unvaccinated students to decide whether to allow for in-person learning. A more detailed evolution of the school protocols in primary and secondary schools is illustrated in Figure 1.5.

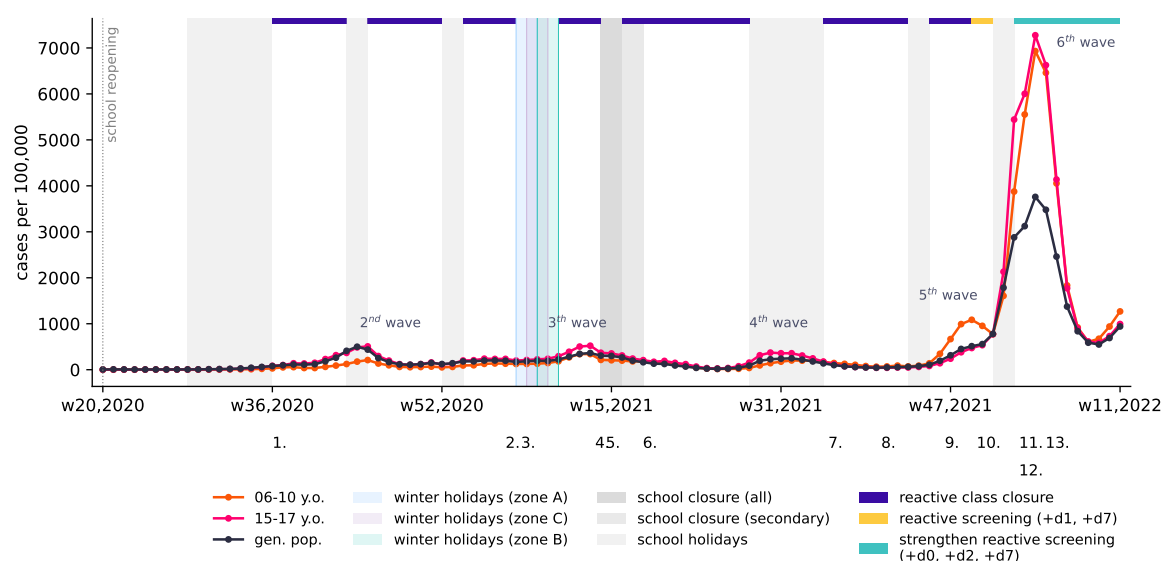
1.3 Surveillance data in community and schools

To monitor the number of cases in the student population, two main initiatives were carried out, which involved:

1. maintaining a national database reporting daily and weekly incidence rates, positivity rates and, the percentage of individuals tested in relation to the number of inhabitants, stratified by school age group;
2. collecting point prevalence data collection on schools in specific time intervals coinciding with the Alpha, Delta, and Omicron waves.

1.3.1 SI-DEP for school ages

SI-DEP (Système d'Informations de DEPistage) platform was made available on May 2020 to systematically collect the results of COVID-19 screening tests (RT-PCR or antigen tests) carried out by authorized laboratories, pharmacies, or health professionals. Data were processed to provide daily or weekly incidence, positivity rate, and rate of tested individuals in the population [70]. Data resolution ranged from municipality to region level. On April 2021, age stratification by school age was also made available [71]. Age classes were constructed according to school levels, namely: under 3 y.o. (nursery), 3 to 5 y.o. (kindergarten),



Protocols

1. Wearing face masks from middle school onwards, class closure from one or two cases of COVID-19, and school closure from three cases.
2. Class closure from the first case. Isolation of one week for contact cases.
3. Class closure from one case in kindergarten, and three cases in primary and secondary schools if it is the historical strain or the Alpha variant. Class closure from one case if the student is infected with the Beta or Gamma variant or if the student is a contact case of one of his parents or a member of his siblings who is a carrier of one of these two variants.
4. Class closure from one case in the areas subject to reinforced measures: Ile-de-France and Hauts-de-France, Seine-Maritime, Eure, Alpes-Maritimes, Aube, Nièvre, and Rhône.
5. Distance learning followed by the introduction of school holidays common to all zones.
6. Class closure from one case on the metropolitan territory.
7. Level 2, class closure in primary schools from the first case.
8. Level 1 (i.e. lifting of barrier measures including the wearing of masks) in 47 departments for which the incidence rate is below the threshold of 50 per 100'000 inhabitants over a five-day period. Class closure from the first case detection.
9. Level 2 except for departments whose incidence rate justifies a higher level. Wearing a mask indoors is compulsory from the first grade onwards, as well as for all staff.
10. Level 3 for primary schools. After a confirmed case, the continuation of classroom learning for students who tested negative. The appearance of three confirmed cases among pupils leads to the closure of the class for seven days.
11. Three mandatory tests every two days for contact cases of a confirmed case to remain in class (PCR or antigenic test for the first, then two self-tests, with statements of negative results).
12. Limitation of the three-test protocol for contact cases to once in a seven-day period.
13. Possibility of performing all three tests by self-testing for contact students. Only one declaration of honour is required

FIGURE 1.4: Weekly incidence in France by age classes and timeline of school protocols applied in primary schools from school reopening in May 2020 to March 2022. Colored lines represent weekly incidence by age classes. The following age classes are considered: 6-10 y.o. corresponding to primary students (in orange) and 15-17 y.o. corresponding to secondary students (in pink). For comparison, the weekly incidence in the general population is reported in dark grey. Weekly incidence refers to France including overseas territories. Vertical grey areas correspond to national holidays or school closures. Colored vertical areas correspond to holidays in specific zones in France. Zone A include: Besançon, Bordeaux, Clermont, Dijon, Grenoble, Limoges, Lyon, Poitiers. Zone B include: Aix-Marseille, Amiens, Caen, Lille, Nancy-Metz, Nantes, Nice, Orléans-Tours, Reims, Rennes, Rouen and Strasbourg. Zone C include: Créteil, Montpellier, Paris, Toulouse et Versailles. Horizontal lines on the top represent testing protocols applied in French primary schools, ranging from *reactive school closure*, *reactive screening*, *strengthen reactive screening*. Source: French Ministry of Education [68]

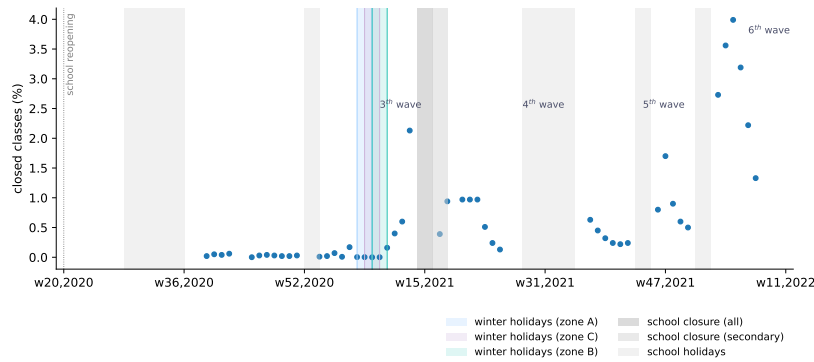


FIGURE 1.5: Percentage of classes closed from school reopening in May 2020 to March 2022 in France. Points represent the percentage of classes closed over the school calendar 2020-2021 and 2021-2022 in primary and secondary schools. From January 2022 onwards, class closures due to confirmed cases among students as well as those due to teacher and staff absence are counted. Vertical grey areas correspond to national holidays or school closures. Colored vertical areas correspond to holidays in specific zones in France. Zone A include: Besançon, Bordeaux, Clermont, Dijon, Grenoble, Limoges, Lyon, Poitiers. Zone B include: Aix-Marseille, Amiens, Caen, Lille, Nancy-Metz, Nantes, Nice, Orléans-Tours, Reims, Rennes, Rouen and Strasbourg. Zone C includes: Créteil, Montpellier, Paris, Toulouse et Versailles [69]

6-10 y.o. (primary school), 11-14 y.o. (middle school) and, 15 to 17 y.o. (high school). Before this more detailed stratification, age classes were divided in 2 subgroups: from 0 to 9 y.o. and 10 to 19 y.o. In the next Chapters, I will use incidence data contained in SI-DEP to inform my model on the expected number of weekly imported cases at school.

1.3.2 Point prevalence data at school during Alpha, Delta, and Omicron waves

Pilot screening campaign during the spring Alpha wave, 2021

Screening initiatives in schools were activated during the third Alpha wave in the Ain, Loire, and Rhône departments in the Auvergne-Rhône-Alpes region in France. The screening was carried out from March 8 to April 2, 2021 (weeks 10-13), and from April 26 to June 7, 2021 (weeks 17-23). Screening in schools was proposed as a measure to identify and isolate undetected cases and reduce within-school transmission. Screenings were on a voluntary basis, as part of surveillance activities in preschool, primary, middle, and high schools. We used data contained information on the number of positive tests, number of tests, and schools to estimate the within-school transmissibility during the Alpha and Delta waves. The screening was performed as a single-point prevalence collection. Only a small number of schools repeated the screening more times. More details are reported in Chapter 2.1.1.

Experimental weekly screening campaign during Fall Delta and Omicron waves, 2021-2022

Weekly screening initiatives were activated in primary schools during the Delta and Omicron waves in the Isère, Puy-de-Dôme, Rhône, and, Savoie departments in the Auvergne-Rhône-Alpes region in France [72]. Screening periods ranged from November 22, 2021, to December 17, 2021 (weeks 47-50), and from January 3 to February 13, 2022 (weeks 1-6). The

main goal was to monitor the prevalence among children and evaluate the effectiveness of the protocol. The collected data included the number of positive tests, total number of tests conducted, as well as the number of students and schools involved. We used the data to estimate the transmissibility of the virus within schools during the Delta and Omicron waves. The screening process was repeated on a weekly basis. Further details are reported in Chapter 2.1.1.

1.4 Vaccination campaign

In France, vaccination was opened to teachers on May 24, 2021 [73]. Adolescents could have access to vaccination starting on June 15, 2021, while children became eligible only on December 22, 2021 [67, 74]. However, large vaccine hesitancy was registered in parents of young children as demonstrated by the low vaccination coverage reached in France in the age class 5-9 y.o. (ca 3% of children had received 1 dose and 2% of children had received 2 doses in week 06, 2022). Higher vaccination coverage was instead recorded in the adult population (ca 90% of adults had received 2 doses in the age brackets 20 – 59 y.o.) and adolescents (ca 79% of adolescents had received 2 doses in the age brackets 12 – 17 y.o.). The most adopted vaccine type was that provided by Pfizer-BioNTech (82% as of 28/10/2021). The booster campaign was opened for adults on December 9, 2021, and for adolescents on January 24, 2022 [75, 76].

1.5 Research questions

In the previous Sections, we saw the difficulties encountered in defining the role of children in the COVID-19 transmission and the actions taken to reintroduce in-person learning after the first lockdown. Nevertheless, the management of COVID-19 in schools continued to be challenging in the academic years 2020-2021 and 2021-2022. The emergence of new variants, the vaccination rollout, and the accessibility of test resources were all elements that influenced the pandemic landscape and required new assessments of the potential school transmission to best guide the efforts. In the subsequent Chapters, I will show how we used mathematical modelling to investigate the mechanisms underlying the transmission of SARS-CoV-2 in schools and support the design and implementation of effective interventions throughout the Alpha, Delta, and Omicron waves. The context and the questions that drove our work are illustrated in Table 1.1, and will be discussed in detail in Chapters 3, 4, and 5.

TABLE 1.1: Questions addressed in this dissertation

Chapter	Article	Context	Questions
3	1	spring Alpha wave and Delta variant emergence in the summer of 2021	1. What is the level of transmission in schools? 2. What is the most effective school protocol for reducing school cases and promoting safe in-person learning in a Delta scenario for winter 2021?
4	2	Omicron variant in early 2022	1. How do the different approaches adopted by Italy, France, and Basel canton respond under high-incidence conditions? 2. What is their cost in terms of test resources?
5	in preparation	Delta and Omicron waves between late 2021 and early 2022	1. Can we infer the school transmission contribution to overall infections in children? 2. How effective is the weekly screening when tested on the field?

Data and model implementation

In this Chapter, I will outline the methodological framework developed to study the spread of SARS-CoV-2 in educational settings and the impact of various interventions, such as reactive strategies and vaccination. The Chapter will begin with an introduction to the epidemiological data used for estimating transmissibility within school settings. Subsequently, I will present the algorithm employed to extend the empirical contact networks from primary and secondary schools, which were used to reproduce interactions among students and teachers based on school type. The focus will then shift to describing the agent-based model and the transmission mechanisms. Finally, I will illustrate the simulated school protocols and the inference framework that led to the estimation of school transmissibility from field screening data.

2.1 Infectious disease data

2.1.1 Field testing data description

As anticipated in Section 1.3.2, local authorities proposed the implementation of school-based testing as part of active surveillance and screening protocols in contexts of higher viral circulation due to the Alpha, Delta and Omicron waves with the aim to:

- monitor the number of infections among students,
- prevent transmission within educational settings through the identification of asymptomatic cases

since students represented a vulnerable population being not yet vaccinated at the time when these initiatives were carried out.

Pilot campaign on March 2021, France

Voluntary screenings were conducted in selected schools within the Ain, Loire, and Rhône departments after in-person classes were resumed following a two-week winter break (weeks 6-7, 2021). Screenings took place from week 10 to week 23 of 2021 (March 8 to June 7, 2021). To contrast the Alpha wave, mitigation measures, including the closure of all schools, were implemented in week 14, 2021 (starting April 5, 2021). Schools remained additionally closed

for the Easter holidays during weeks 15 and 16 of 2021. Primary and secondary schools resumed in-person classes in weeks 17 and 18 of 2021, respectively. Consequently, school-based testing was suspended from weeks 14 to 16, 2021, and resumed during week 17, 2021 (week 18 for secondary schools).

PCR tests on saliva samples were proposed in pre-schools and primary schools, and anterior nasal lateral flow device (LFD) tests in middle and high schools.

A total of 1,331 screenings were conducted across the three departments. Each screening was associated with information on the screening date, school name, administrative division, Unique Identification Code (UAI code), number of tests offered to students and staff members, number of tests used, and test results. Schools were categorized into four types (preschool, primary, middle, and high school) based on their UAI code. After removing unidentified or unspecified UAI or entries with missing data on the number of tests, a final sample of 779 screenings in 683 schools with distinct UAI codes was considered in the analysis. The sample included 94 preschools, 427 primary schools, 158 middle schools, and 4 high schools, encompassing a total population of 209,564 students and 18,019 personnel. At the departmental level, this comprised 152 screenings in the Ain department (representing 18% of the schools), 212 screenings in the Loire department (representing 31% of the schools), and 415 screenings in the Rhône department (representing 52% of the schools). The number of screened schools by type over the weeks is illustrated in Figure 2.1. A small proportion of schools conducted multiple screenings, with 13% of schools conducting the screening twice and only 1% conducting it three times, which was the maximum frequency during the study period.

The observed adherence was computed at each screening as the ratio between the number of screened individuals and the number of individuals who were offered to be screened. Higher adherence was estimated in primary schools compared to secondary schools and in students compared to school personnel. The median adherence obtained for the primary and secondary schools over the full study period were used to inform the model for the winter Delta scenario in Article #1, see Figure 2.2

We focused our analysis on data collected during the initial phase of the third wave, specifically from week 10 to week 13 of the year 2021. This time frame was selected to ensure that the data were collected before the reactive school closure and the implementation of lockdown measures when the effective reproductive number in the community (R_t) exceeded 1. Additionally, we excluded data from pre-primary school screenings due to the lack of information on contact patterns necessary to describe interactions in such settings. Furthermore, we removed screening entries from the dataset that had missing data on test results. The following inclusion criteria needed to be satisfied in order to be included in the analysis:

1. Screenings were performed in the study period from week 10 to 13 of 2021.
2. Screenings involved at least 5 screened schools and 500 screened students per department in a given week per school type (primary or secondary) to ensure enough statistics.

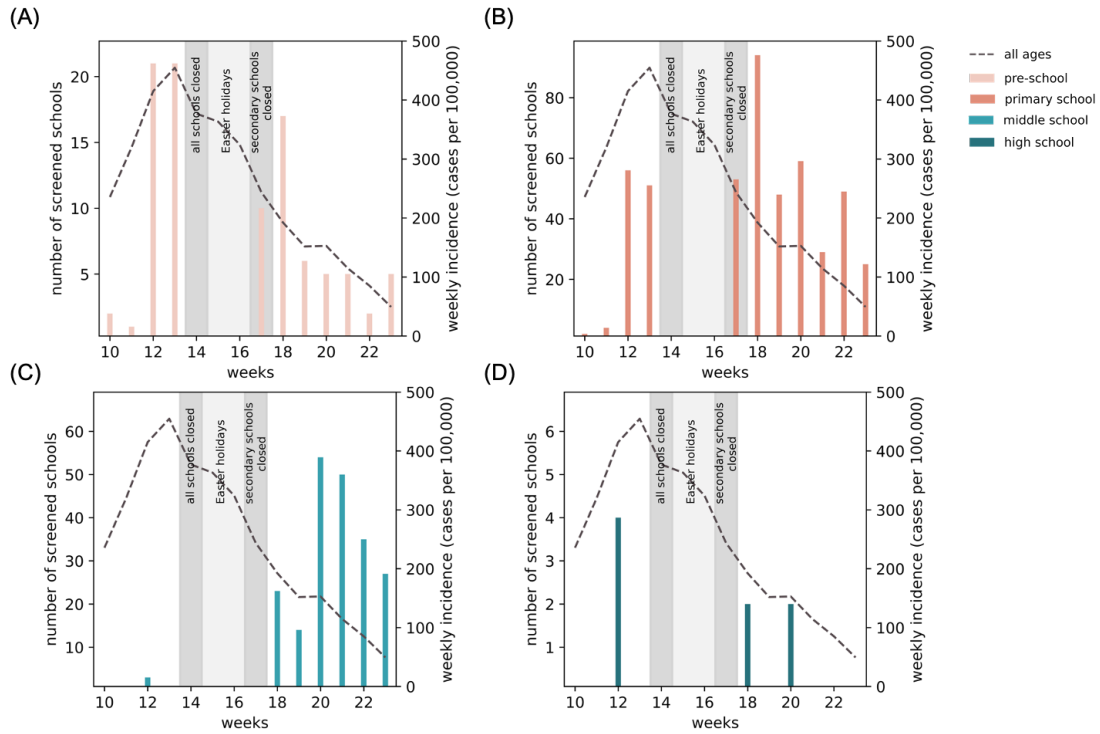


FIGURE 2.1: Number of screened schools in pre-schools (A), primary schools (B), middle schools (C), high schools (D) by week. Each panel reports the weekly incidence (cases per 100,000) over time from community surveillance in the 3 departments under study (dashed lines); data refer to all ages; data from Geodes. The vertical grey shaded areas correspond to the school closures in the period.

3. Adherence per school larger than or equal to 50% to ensure that the majority of the school population was screened

Through the inclusion criteria, 71 primary schools were selected for a total of 12,146 tested students in weeks 12 and 13 in all three departments. Screening data in secondary schools were excluded because of limited participation (2 schools with 45 tested students in the Loire, and 5 schools with 341 tested students in the Rhône department in w12). The number of tested students by department and week is shown in Table 2.1.

TABLE 2.1: Number of tested students during the pilot screening campaign of March 2021 included in the analysis through the reference inclusion criteria

Department	W12	W13
Ain	1719	1013
Loire	807	542
Rhône	4946	3119

Experimental weekly screening in 2021-2022, France

A systematic screening program was piloted in selected primary schools across four departments in France: Isère, Puy-de-Dôme, Rhône, and Savoie. The trial took place between weeks 47 and 50 in 2021 (from November 25, 2021, to December 19, 2021) during the Delta variant circulation [72]. Throughout this period, screenings were proposed every Monday.

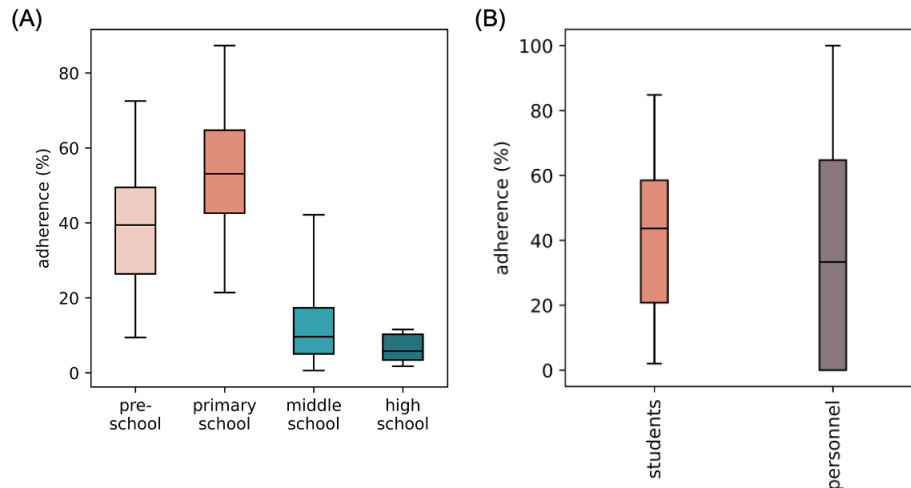


FIGURE 2.2: Box plots represent the median (line in the middle of the box), interquartile range (box limits) and 2.5th and 97.5th percentiles (whiskers) of observed adherence by students type and role among students (from pre-primary to high school) and personnel

The screening activities were interrupted in weeks 51 and 52 due to the Christmas holidays. In the weeks 01 and 06 of 2022 (from January 03, 2022, to February 13, 2022), coinciding with the emergence of the Omicron variant, a second round of screening was performed on a subset of the schools previously involved in the initial experimentation.

The screening was voluntary with parental consent and involved PCR tests on saliva samples for primary students. In total, 28,643 tests were conducted in 25 primary schools across the four departments during the entire period. The recorded data included the screening week, school name, administrative division, number of students present during screening, number of tests proposed, and number of positive tests. Entries with zero test counts were excluded from the analysis. At the departmental level, 3653 tests were conducted in the Isère department (involving 0.7% of primary schools), 1230 tests in the Puy-de-Dôme department (involving 0.9% of primary schools), 20,577 tests in the Rhône department (involving 1.3% of schools), and 3,183 tests in the Savoie department (involving 2.9% of schools). The number of screened schools per department across the weeks is presented in Figure 2.3.

The observed adherence was computed at each week as the ratio between the total number of tests and the total number of students present on the day of the screening by departments. Higher adherence was estimated in the Rhône department compared to others, and in the second round compared to the first one. Weekly estimates of adherence were used to inform the model for the Delta and Omicron analysis in Article #3.

Inclusion criteria were established to ensure enough statistics of the screening data used in the analysis. Specifically, for each study week, it was required that:

1. Screenings involved at least 5 screened schools.
2. 500 students were screened per department

Based on the specified criteria, we selected a total of 18 primary schools over the first and second rounds. For the first round, this resulted in 17 distinct primary schools and 10,297

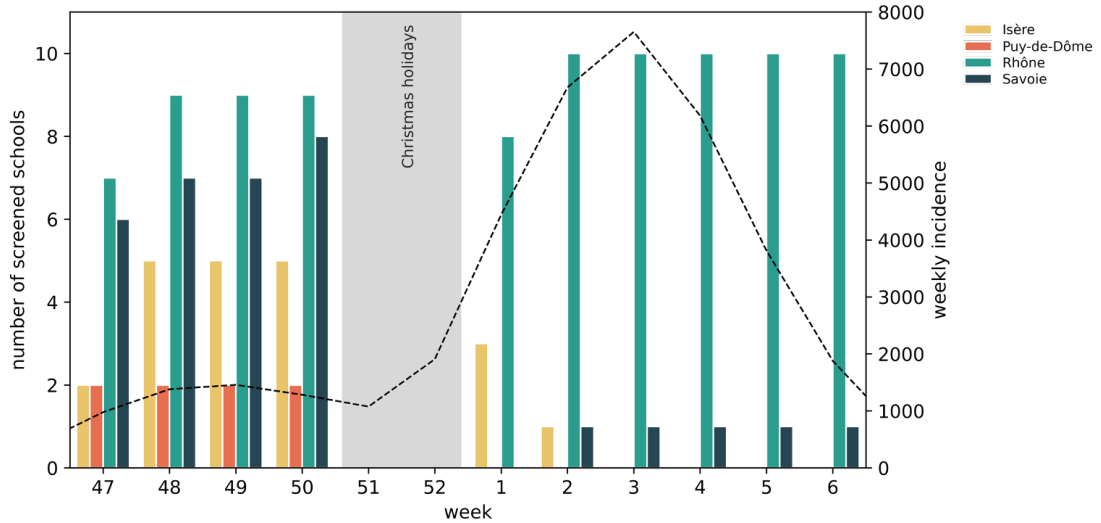


FIGURE 2.3: Weekly incidence and number of screened schools over time by departments during the experimental weekly screening in winter 2021-2022. Number of primary screened schools in the Isère (yellow), Puy-de-Dôme (orange), Rhône (green) and, Savoie departments (blue) by week. Dashed line represents the weekly incidence (cases per 100,000) over time for the age class 6-10 y.o. from community surveillance data in the 4 departments under study; data from Geodes. The vertical grey shaded area correspond to the Christmas holidays.

tests during weeks 47 and 50 of 2021 in the Rhône and Savoie departments. For the second round, the criteria selected 10 primary schools, with a total of 13,143 tests conducted during the weeks from 01 to 06 of 2022 in the Rhône department. We excluded screening data from the departments of Isère, Puy-de-Dôme, and Savoie due to their limited participation in the screening. The number of tested students by department and week is shown in Table 2.2. Adherence to screening over time is shown in Figure 2.4.

TABLE 2.2: Number of tested students during the experimental screening in winter 2021-2022 included in the analysis through the reference inclusion criteria

Department	W47	W48	W49	W50	W01	W02	W03	W04	W05	W06
Rhône	1369	1847	2111	2107	1769	2246	2514	2503	1827	2284
Savoie	537	692	804	830	/	49	67	79	70	55

2.2 Temporal contact network

The frequency and duration of contacts between individuals greatly influence the spread of a communicable infectious disease such as COVID-19, shaping the transmission dynamics of the virus. Information on contacts in children and adolescents at school can help to characterize mixing in educational settings, avoid assumptions, identify possible transmission routes, and evaluate the effectiveness of control measures targeting contacts. In the following sections, I will present the properties of two empirical contact networks that were obtained from data collected through wearable sensors as part of the Sociopatterns project [77]. These networks represent the first element of our methodological framework and the foundation of our transmission model.

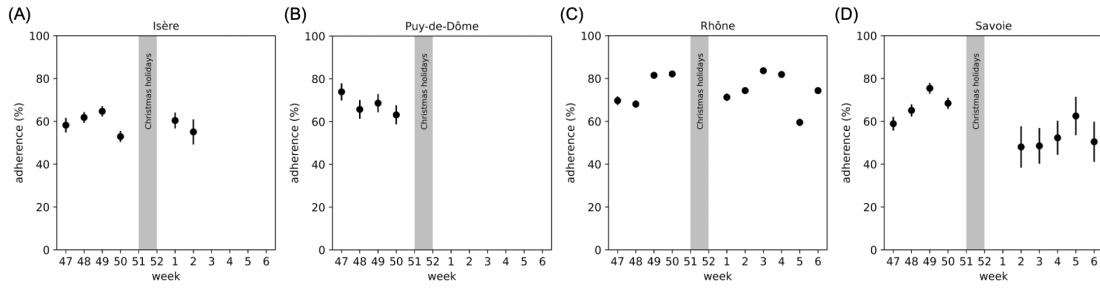


FIGURE 2.4: Observed adherence to weekly screening over the first and second round of experimentation by departments in winter 2021-2022. Points represent the observed adherence to weekly screening over the first and second round of experimentation in winter 2021-2022 in the selected schools. Lines represent 2.5th and 97.5th percentiles.

2.2.1 Empirical contact networks

Empirical data from wearable radio frequency identification devices (RFID) were used to characterize face-to-face proximity contacts between individuals in two educational settings in France, namely a primary school [78] and the fourth year of a secondary school (classes préparatoires in the French system) [79]. During the data collection period prior to the COVID-19 pandemic, individuals were requested to wear RFID sensors on their chests, which were embedded into wearable and non-invasive badges.

These sensors enabled the exchange of ultra-low power radio packets when individuals wearing them were in close proximity to each other (approximately 1 to 1.5 meters). This range was selected to represent close-range encounters during which transmission of communicable diseases could occur (i.e. through coughing, sneezing, or direct hand contact). A contact between two individuals was established if their badges exchanged at least one radio packet within a 20-second time window. If no exchange of radio packets occurred, the contact event was considered interrupted. Once a contact was established, it was considered ongoing as long as the devices continued to exchange at least one packet at subsequent 20-second intervals. Consequently, each dataset consisted of a list of contacts between pairs with a temporal resolution of 20 seconds.

The contact data were then aggregated into time intervals of $\Delta t = 15$ minutes, based on the guidelines set by the European Centre for Disease Prevention and Control (ECDC) [80] which classified a high-risk exposure as any contact with a positive person to COVID-19 lasting $\Delta t = 15$ min (or more). This aggregation resulted in a weighted network of interactions for both types of schools within each 15-minute time window. Each node in the network represented an individual, and a link between two nodes indicated that those individuals had been in contact at least once during the time window. The weight of each link was determined by the fraction of time spent in contact during the 15-minute interval.

Primary school

The primary school dataset included 232 participating students (aged 6-11 years, representing 96% coverage) and 10 teachers (representing 100% coverage) across 10 classes (with a mean class size of 23.2 students). Data were collected over two days in a primary school in

Lyon, France, in October 2009 during school hours; specifically from 8:45 a.m. to 5:20 p.m. on the first day and from 8:30 a.m. to 5:05 p.m. on the second day. Contacts outside of these time intervals were not recorded. Radio receivers (RFID readers) were placed in all the classrooms, the canteen, the stairways, and the playground. However, no information was gathered regarding contacts outside the school premises or during sports activities.

The analysis of network properties revealed that children had a significant number of distinct contacts throughout the day, interacting with almost all their classmates (83% of the class). Additionally, there were approximately 50% more links between classes compared to the number observed within classes. In terms of contact duration, children spent more time interacting within their own class than outside of it, and their contacts were longer compared to teachers. These aspects will be important for interpreting the results in the next Chapters.

Secondary school

The secondary school dataset included 325 participating students (aged 17-18 years, representing 86.3% coverage) from 9 classes (with a mean class size of 35.8 students). The classes belonged to the second year of a secondary school in Marseille, France, and were divided into three groups based on their specializations. Data collection took place over four days in December 2013. Similarly to the primary school dataset, RFID readers were installed throughout the high school, while contacts occurring outside the school premises were not measured.

By analyzing the number of contacts, students in the secondary school were found to establish interactions with approximately 33% of their classmates. Moreover, there were 75% fewer connections between classes compared to within classes. Regarding contact duration, similarly to the primary school dataset, adolescents spent more time interacting with their classmates than with students from other classes.

2.2.2 Synthetic temporal extension

Synthetic networks were constructed to extend the duration of the school contact datasets beyond their limited temporal scope while preserving the observed characteristics of the networks. The method proposed here aimed to accurately replicate key features such as class structure, within-class, and between-class links, contact duration variability, and similarity across days (Figure 2.5). For the sake of simplicity and conciseness, I will focus on the primary school case only in this thesis. However, a similar procedure was employed to create a temporal extension of the *classes préparatoires* dataset. More detailed descriptions are available in the Supplementary Material of Article #1 [6].

The algorithm for generating synthetic copies of the empirical primary school network can be synthesized in the following steps:

1. For each class, a synthetic network of contacts is generated as a random graph with the same number of within-class links as observed in the empirical one.

For each pair of individuals in contact in the synthetic copy, three cases can occur:

- the pair was in contact on both days of the empirical data (i.e., they had a repeated link across the two empirical days), with an overall contact duration of w_1 on the first day and w_2 on the second day. Then, a contact duration taken at random between w_1 and w_2 is assigned with a probability of p ;
 - the pair was in contact on one of the two days of the empirical data. Then, a contact duration is randomly taken from the daily contact durations measured on the empirical day in that class.
 - the pair was not in contact in the empirical data, then a random value taken from the set of daily contact durations measured in the empirical dataset over the two days is randomly assigned.
2. For each pair of classes in the synthetic version, an equal number of inter-class links are generated as in the empirical data. These links can either be taken from the empirical data or added as new links. When adding a link, there is a chance that an existing link will be chosen, with a probability of p' . On the other hand, there is a probability of $1 - p'$ that a random link will be added, with a duration drawn from the observed duration values between this pair of classes.

The quantities p and p' were computed from the average similarity in order to best reproduce the properties of the empirically observed interactions.

For the simulations of SARS-CoV-2 spread during the Alpha period in Article #1, 90 daily copies were created, corresponding to an entire school trimester. For Article #2 in Chapter #3, as many copies as needed to cover 12 weeks were instead produced. Finally, for Article #3 in Chapter 4, 42 daily copies were considered.

2.3 Transmission model

2.3.1 Disease progression

I developed a stochastic agent-based model to simulate the spread of SARS-CoV-2 in educational settings by leveraging the school contact networks and their temporal extension. The model includes different epidemiological states through which individuals can transition during the course of the infection, as illustrated in Figure 2.7. Susceptible individuals (S) can become exposed (E) when in contact with an infectious person. While they are exposed, individuals cannot transmit the infection. After an average latent period τ_E , they enter a prodromic phase (I_p) where they can spread the disease without showing symptoms. Next, individuals can either remain asymptomatic (I_{sc}) with a probability of p_{sc} or develop clinical symptoms (I_c) with a probability of $p_c = 1 - p_{sc}$. Individuals in the prodromic and subclinical compartments are considered less infectious and are undetected unless tested [81, 82, 83]. Individuals showing clinical symptoms can instead be identified with a probability p_d

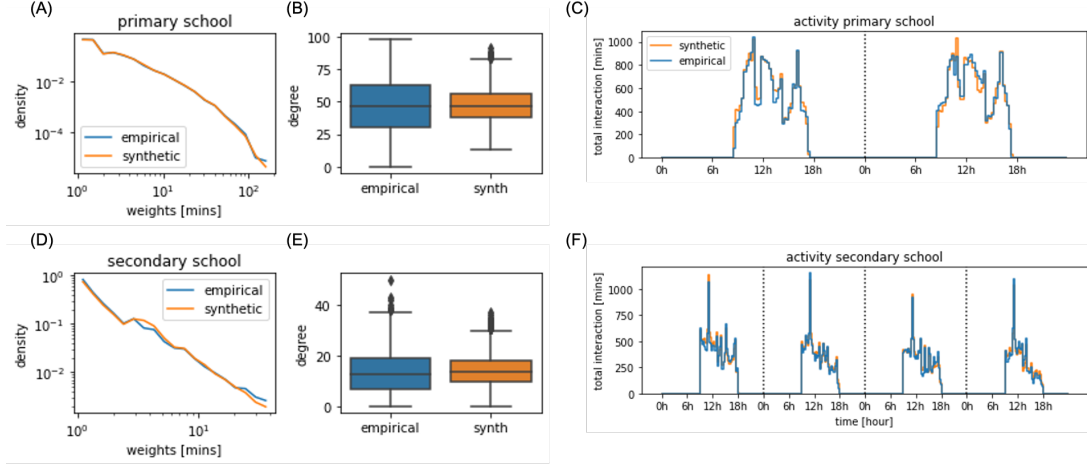


FIGURE 2.5: Distributions of daily contact durations, degree distributions, and timelines of contact durations for the empirical and synthetic data. A. Distributions of daily contact durations for the empirical and synthetic contact networks for the primary school. B. Degree distributions for the empirical and synthetic contact networks for the primary school. The central horizontal line gives the median value of the distribution, the box shows the quartiles of the data sets, and the whiskers show the rest of the distributions. C. The line gives the value of the total time in contact for all individuals during 15-minute time windows. D. as in A for secondary school. E. As in B for secondary school. F. As in C for secondary school. The comparison is limited to the first-year students, as only those are present in the empirical data.

and isolated for a fixed period Δq if they test positive through symptom-based testing. If teachers need to isolate because positive, they are temporarily replaced with a susceptible individual (S) until they test negative or for a maximum of 2 weeks. The probabilities p_{sc} and p_d are age-dependent and generally smaller for students than for teachers [24, 83, 84, 85, 86, 87, 88]. After the infectious phase given by the sum of the prodromic and symptomatic (asymptomatic) periods $\tau_I = \tau_{I_p} + \tau_{I_{c/sc}}$, individuals enter a transient phase (R_+) where they are no longer infectious but can still be detected as positive by more sensitive tests, such as PCR tests, because of a residual viral presence in the upper respiratory tract [21, 89, 90]. Finally, individuals move to the recovered compartment (R). When the Omicron variant is considered (see Articles #2 and #3), reinfection is possible. In this case, individuals previously infected by variants different from Omicron may acquire the infection again (S^*) but with a reduced probability because of the partial protection provided by the natural infection [91, 92] (see Subsection 2.3.2).

The time spent at each stage ($\tau_E, \tau_{I_p}, \tau_{I_c}, \tau_{I_{sc}}$) was informed by empirical distributions. The parameters used to inform the model are provided in Section 2.3.3.

The transmission model is further stratified to incorporate vaccination by labelling each individual as unvaccinated, fully vaccinated (2 doses), or boosted (2 doses followed by a booster shot). Vaccination was modelled to protect against infection, transmission, and clinical symptoms upon infection. Vaccination works by lowering the relative susceptibility (σ) and transmissibility (r_β). The reduction in susceptibility and transmissibility depends

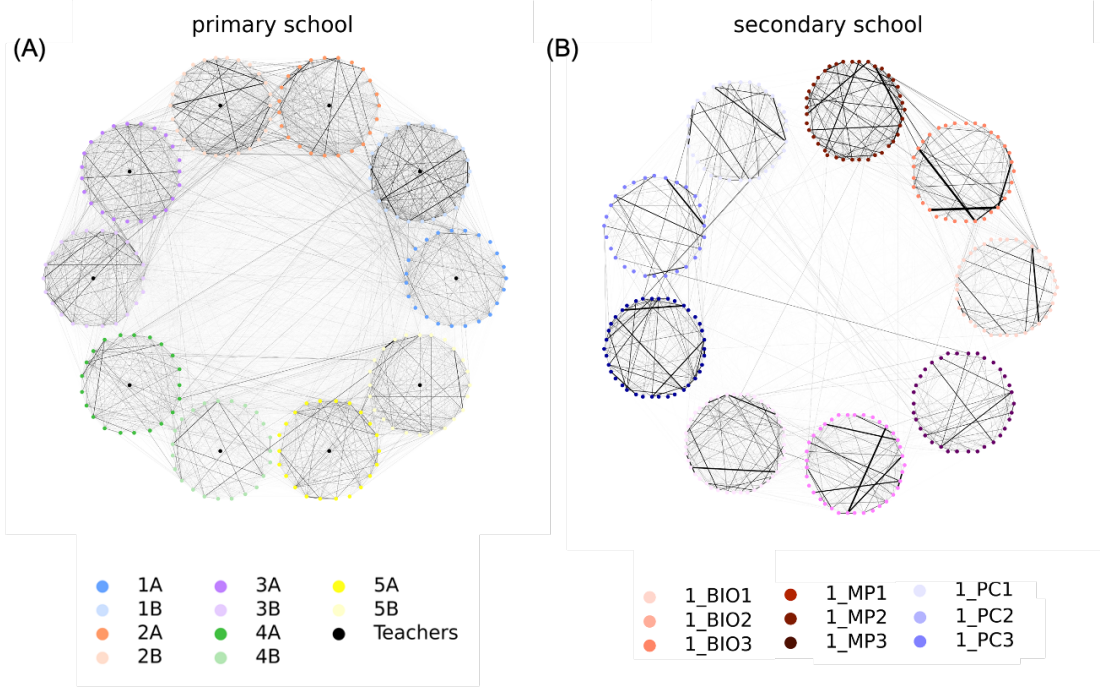


FIGURE 2.6: Snapshots of the contact networks for the primary and secondary schools. Visualization of the primary and secondary school networks aggregated over two days. Nodes represent teachers and students, each circle represents a class, and links represent contacts, with the thickness representing the contact duration.

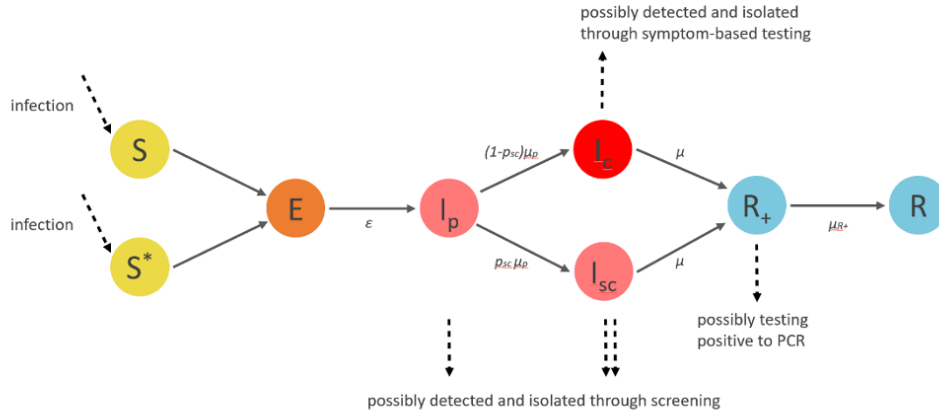


FIGURE 2.7: Scheme of COVID-19 progression. The epidemiological state of an individual at a given time corresponds to one of the following compartments: susceptible S, S^* , exposed E , prodromic I_p , clinical I_c or asymptomatic I_{sc} , and recovered (R_+ or R). The quantities $\epsilon, \mu_p, \mu, \mu_{R+}$ represent the transition rates from one state to the other.

on the protection provided by the vaccine against infection and transmission (i.e. the vaccine effectiveness VE_{inf} and VE_{transm}), respectively. For vaccinated individuals, the relative susceptibility (σ_{vax}) and transmissibility ($r_{\beta, vax}$) are given by:

$$\sigma_{vax} = (1 - VE_{inf})\sigma$$

$$r_{\beta,vax} = (1 - VE_{transm})r_{\beta}$$

Furthermore, vaccination affects the probability of transitioning into the I_{sc} and I_c compartments (as shown in Figure 2.8), reducing the risk of developing symptoms once vaccinated individuals are infected. More specifically, the probability of developing symptoms for vaccinated individuals is defined as follows:

$$p_{c,vax} = (1 - VE_{symp|inf})p_c$$

where $VE_{symp|inf}$ denotes the vaccine effectiveness against symptoms given an infection. Consequently, the probability to stay asymptomatic is given by

$$\begin{aligned} p_{sc,vax} &= 1 - p_{c,vax} = 1 - (1 - VE_{symp|inf})p_c = \\ &= 1 - (1 - VE_{symp|inf})(1 - p_{sc}) = \\ &= p_{sc} + VE_{symp|inf} - VE_{symp|inf} * p_{sc} = \\ &= (1 - VE_{symp|inf})p_{sc} + VE_{symp|inf} \end{aligned}$$

The estimates of VE were updated over time and by variants according to the most recent evidence in the literature (see Section 2.3.3).

When Alpha and Delta variants are considered, as in Articles #1 and #2, individuals can not change their vaccination status and the coverage remain fixed over the simulated time. Instead, a dynamic vaccination rollout is modelled to reflect the faster waning in the protection provided by the vaccination in children against the Omicron variant compared to the previous ones [93, 94] (see Article #3, Chapter 5).

The estimates on vaccination coverage over time in children, adolescents, and teachers in France were informed by SpF data [95] while the estimates on the European coverages were derived by the ECDC tracker platform [96].

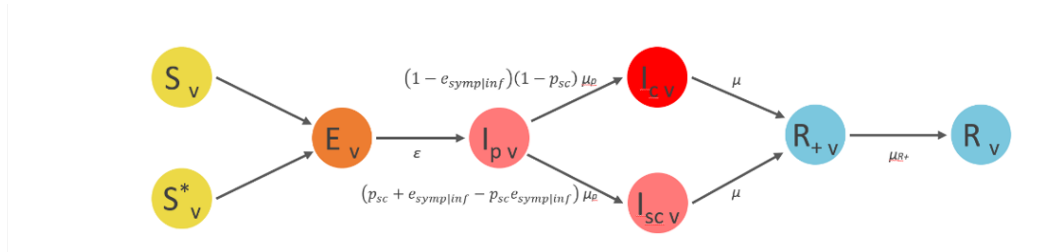


FIGURE 2.8: Scheme of COVID-19 progression with vaccination.

2.3.2 Infection probability

Transmission events are modelled considering a dual mechanism. Firstly, we consider transmission events due to interactions within schools, namely interactions among students and between students and teachers. All these interactions are explicitly outlined in the specific school network. However, students and teachers are also susceptible to contracting COVID-19 via interactions that take place outside the school premises. This second case represents the circumstance in which the virus is introduced from the community into the school. Therefore, we include a certain number of introductions over the course of the simulations (cases generated outside the school context). This allows us to simulate how they contribute to the spread once penetrate into school. In the subsequent sections, I provide the mathematics behind these two events.

Within school transmission

Within-school transmission is modelled with an algorithm based on rejection sampling [97]. At each discrete time step Δt of 15 minutes, the algorithm evaluates the interactions between susceptible individuals (S) and individuals in one of the possible infectious states (I_p , I_c , and I_{sc}). For each susceptible-infectious pair, the algorithm computes the probability (p) associated with the occurrence of a transmission event between these individuals. The transmission probability p is defined in the following way

$$p = \beta * \sigma_s * r_\beta * w * \Delta t \quad (2.1)$$

and results proportional to the following quantities:

- the transmission rate per contact per unit time β
- the age-dependent susceptibility σ_s
- the age and stage-dependent transmissibility r_β
- the duration of the contact w within the time step Δt as reported in the network

Then, a random number $r \in [0, 1)$ is selected from a uniform distribution and compared to the probability p . Based on the value of r , the transmission event is accepted or rejected. In particular, if $r < p$, we update the state of the susceptible individual S in the exposed state E , otherwise nothing occurs. A transmission event is possible as long as individuals are not in quarantine or isolation. In the latter case, individuals are temporarily denoted as isolated nodes within the school contact network. Once an individual is infected, spontaneous transitions between successive compartments (from E to I_p , etc.) are evaluated at each time step within and outside school hours. The time spent in each compartment followed empirical distributions, as reported in Section 2.3.3.

In Equation 2.1, the school transmission rate per contact per unit time β is the unknown parameter to infer by fitting the model to the data from screenings in the specific period under study (see Section 2.5). The transmission probability p is smaller when in contact with

prodromic and asymptomatic individuals compared to symptomatic individuals, since they are considered less infectious [81, 82, 83, 98]. The probability of transmitting and receiving the infection decreases in vaccinated individuals according to the reduced transmissibility ($r_{\beta, vac}$) and susceptibility (σ_{vac}) of these individuals compared to the unvaccinated ones. When reinfection is modelled (Article #2 and Article #3), we consider that the probability to get the infection in individuals who have already experienced COVID-19 (S^*) is partially reduced [91]. Consequently, if $p_{reinfection}$ is the protection against the reinfection, the susceptibility parameter in Equation 2.1 can be expressed as follows:

$$\sigma_{S^*} = \sigma_S * (1 - p_{reinfection})$$

In each Article, we performed a sensitivity analysis to assess the impact of reduced transmissibility and susceptibility in children and adolescents.

Imported cases from community

Our modelling framework primarily focuses on interactions within the school environment, as the RFID sensors data specifically capture interactions within schools. Nevertheless, transmission events can also occur beyond the school setting when teachers and students come into contact with family members or the community. To model this type of event, we consider a weekly influx of infected individuals from the community into the school environment. This is accomplished by selecting a random time step and day outside of school hours and moving the status of some individuals in the networks from the susceptible (S) status to the exposed (E) status. The weekly number of infections introduced at school is inferred from the community prevalence in specific age classes (children, adolescents, and adults) [99] and accounts for factors such as the probability of detection and the school size [100, 101], as explained below. We used as a data source the GEODES platform by Santé publique France for the weekly departmental and age-specific incidences (see Section 1.3.1). We distinguish two main cases:

- imported cases (or introductions) at the school reopening;
- imported cases (or introductions) during school sessions;

At the school reopening. When schools are closed, transmission chains within the school are interrupted. Consequently, at school reopening, community incidence accounts exclusively for introductions. Therefore, the expected number of COVID-19 introductions after school holidays or closures in a specific age class (n_{age}) and given department (dep) can be modelled as a function of the community prevalence $preva_{age, dep}(w)$ by assuming a binomial distribution

$$Intro_{age, dep}(w) \sim Bin(n_{age, dep}, preva_{age, dep}(w)) \quad (2.2)$$

In turn, the prevalence $preva_{age, dep}$ can be derived from the community surveillance incidence $i_{age, dep}$, as follows

$$preva_{age}(w) = i_{age}(w - 1) / p_{det, age}$$

Here, a probability of detection $p_{det,age}$ is incorporated to account for potential under-reporting of asymptomatic infections and the limitation of the surveillance system to confirmed cases only. This correction compensates for cases that might go unreported due to a lack of symptoms. Additionally, we consider that the number of introductions at school in week w is linked to the proportion of individuals in that school who receive positive test results in week $w - 1$ and are still infectious within the limit of a typical infectious period of about 7 days.

In the formula 2.2, the size n_{age} varies with school type (primary vs. secondary) and role (students vs. teachers). The probability of detecting COVID-19 infection based on symptoms is age-dependent and informed by the literature in Articles #1 and #2 [87, 88, 102]. Additional values of the detection probability were explored for sensitivity analysis. In Article #3, the probability $p_{det,age}$ was estimated together with the transmission rate β (see Section 2.5).

During school sessions. In the weeks following the school reopening and during active class sessions, the incidence rate $i_{age,dep}$ represents a combined measure of infections introduced from outside the school setting and those that occurred within the school premises. To estimate the expected number of introductions in a given week w , we adapted the approach used in [103], which distinguished between local and imported cases. More specifically, we refined the count of weekly introduction $Intro_{age,dep}(w)$, as obtained in 2.2, by multiplying for a factor k to discount the contribution of within-school transmissions as estimated by the model.

$$k = \frac{Intro_{age,dep}(w - 1)}{Intro_{age,dep}(w - 1) + School_{age,dep}(w - 1)}$$

This decomposition of school-related and community-related infections allows us to account for both internal and external sources of infections in schools. We implemented this approach within the inference framework to estimate the parameter β in Articles #1 and #3. Instead, when we considered interactions with the community under the Delta scenario explored in Article #1, we kept the number of imported cases constant since we could not inform the model about the exact incidence experienced during the winter of 2021 in advance. Therefore, we explored different community incidence rates and corresponding introductions to simulate different conditions of introductions (from low to very high) throughout the simulations.

For the Omicron analysis in Article #2, the initial number of introductions was inferred by fitting the model to the community surveillance data, given the within-school transmission rate $\beta_{Omicron}$ computed starting from the estimated β_{Delta} in Article #1 and using the corresponding transmission advantage.

2.3.3 Parametrization

Epidemiological parameters

To accommodate a non-exponential distribution of the time spent in each disease stage (E , I_p , I_c , and I_{sc}), we subdivided these compartments into sub-compartments [104]. This subdivision enabled a more accurate representation of the different lengths of stay in each infection stage for each individual. Figure 2.9 shows the empirical distributions used in Article #1. The time spent within each stage changed with variants to reflect their specific characteristics. For example, in the studies related to the Omicron variant, a shorter latent period was considered compared to the Delta and Alpha variants. This adjustment was made to effectively replicate the accelerated dynamics and shorter generation time of this variant compared to the Alpha and Delta variants. In Article #2, the average latent period was shortened by 0.5 days to model the Omicron variant characteristics. Additionally, in Article #3, we revised the latent period to accurately reproduce a new available estimation of the generation time, as reported in [105]. We also considered that viral shedding could last up to $\tau = 24.5$ days in Articles #1 and #2 [89]. This implied that individuals could stay in the R_+ compartment on average for a time $\tau_{R_+} = \tau - \tau_{I_p} - \tau_{I_c}$. Then, we revised this value in Article #3 to account for evidence suggesting a more rapid viral clearance with the emergence of the new variants, typically requiring 10 days to decline from peak to undetectable viral level [21].

In our analysis, we considered that primary school children and adolescents had a relatively lower susceptibility and transmissibility compared to adults (see Chapter 1). The parameter values used to parameterize the model in Article #1 are listed in Table 2.3. We used the same estimates for the subsequent investigations in Article #2 and Article #3. However, as new evidence emerged, larger values of relative susceptibility and transmissibility were tested for sensitivity analysis [28, 106].

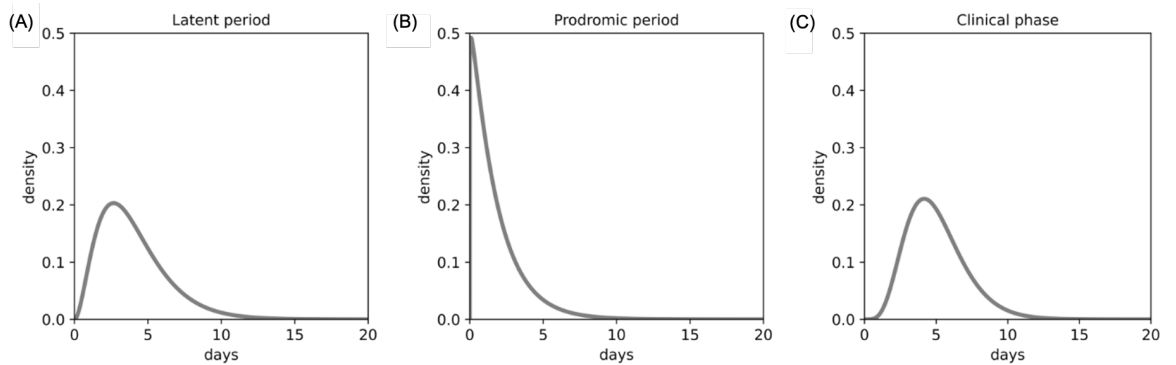


FIGURE 2.9: (A) Gamma distributed latent period (τ_E) with mean=4.00 days and std=2.30 days (shape=3.00, scale=1.33). (B) Gamma distributed prodromic period (τ_{I_p}) with mean=1.80 days and std=1.75 days (shape=1.05, scale=1.71). (C) Gamma distributed clinical phase (τ_{I_c}) with mean=5.00 days and std=2.03 days (shape=6.00, scale=0.833). Distributions of disease state durations are assumed to be the same for students and teachers. Estimates from [107]

The transmission rate β^{Alpha} was estimated by fitting the model to screening data gathered during the pilot screening campaign, as described in Subsections 1.3.2 and 2.1.1 (see

TABLE 2.3: Epidemiological parameters used in the Delta scenario contained in Article #1.

Variable	Description	Value	Source	Sensitivity
σ_S	relative susceptibility to infection compared to adults	0.5 in primary students 0.75 in secondary students	[108, 109, 110]	– 1
p_{sc}	probability of subclinical infection	0.8 for students 0.5 for teachers	[84, 85, 86, 111, 112]	– –
β	transmissibility per contact per unit time with maximum likelihood (MLE)	–	–	–
ϕ^{Delta}	transmissibility advantage of Delta compared to Alpha variant	79%	[113]	52%, 110%
$\phi^{Omicron}$	transmissibility advantage of Omicron compared to Delta variant	30%	[114]	80%
r_β	relative transmissibility in prodromic and sub-clinical stages	0.55 if I_p or I_{sc}	[81, 82, 83, 115]	0.4, 0.75
$r_\beta^{children}$	relative transmissibility of children	0.63	[29]	0.8

TABLE 2.4: Immunity estimates

Role	Value	Variant	Article	Source
primary students	10%	Alpha	#1	[116]
	25%	Delta	#1	assumed
	40%	Omicron	#2	assumed
	30% 35%	Delta Omicron	#3 #3	[117] assumed
secondary students	12%	Alpha	#1	[116]
	25%	Delta	#1	assumed
teachers	15%	Alpha	#1	[116]
	25%	Delta	#1	assumed
	40%	Omicron	#2	assumed
	50% 55%	Delta Omicron	#3 #3	[117] assumed

Section 2.5 for the inference framework). For the Delta scenario contained in Article #1, the transmission rate was obtained starting from the estimated β^{Alpha} by using the following relationship:

$$\beta^{Delta} = (1 + \phi^{Delta})\beta^{Alpha}$$

Here, ϕ^{Delta} represents the transmission advantage of the Delta variant relative to the Alpha variant. Analogously, a comparable approach was taken for the Omicron variant in Article #2, wherein the transmission advantage over Delta was considered. The values used for the transmission advantage for both the Delta and Omicron variants were informed from the literature [113, 114]. In Article #3, the transmission rates β^{Delta} and $\beta^{Omicron}$ were newly estimated from the field as more recent screening data became available under the experimental weekly screening in winter 2021-2022 (Subsections 1.3.2 and 2.1.1).

Initial immunity. Initial immunity values were informed by seroprevalence estimates when available or assumed otherwise (see Table 2.4).

Vaccine effectiveness

In the simulations, fully vaccinated individuals (those with two vaccine doses) or individuals who had received booster doses were considered. The vaccine effectiveness (VE) estimates referred specifically to these two situations and to the Pfizer vaccine, which was mostly adopted in France (82% as of October 28, 2021 [99]). Vaccination was modelled in order to lower the risk of infection, transmission, and the development of symptoms among vaccinated individuals. The extent of this reduction depended on the vaccine effectiveness against each of these cases, namely VE_{inf} , VE_{transm} , and VE_{symp} . The effectiveness against symptoms (VE_{symp}) depends on the interplay of two components:

- the effectiveness against infection (VE_{inf})
- the effectiveness against symptoms given the infection ($VE_{symp|inf}$)

The relationship between these two components can be expressed as follows:

$$1 - VE_{symp} = (1 - VE_{inf})(1 - VE_{symp|inf})$$

Therefore, the effectiveness against symptoms given the infection $VE_{symp|inf}$ is given by the following equation:

$$VE_{symp|inf} = \frac{VE_{symp} - VE_{inf}}{1 - VE_{inf}}$$

In our analysis, vaccine effectiveness values were taken from studies conducted during the Delta and Omicron variants [93, 118, 119, 120, 121, 122, 123, 124, 125]. Initially, we studied the impact of vaccination on adults, adolescents, and children in the winter Delta scenario contained in Article #1. The considered estimates accounted for age difference (adolescents vs. adults and children vs. adults) and waning effects in VEs after the second vaccine dose or booster dose. In particular, given that the vaccination of teachers started on May 24, 2021, and that 50% of adults within the 18-59 age group were vaccinated by late July 2021 (see Section 1.4), we considered an average delay of approximately 3-4 months post full vaccination for the Delta analysis. Under this assumption, the effectiveness against infection for the adult population (18-64 years) was set to 73% against the Delta variant [118], in line with [121]. Similarly, we considered 70% of VE_{symp} within the adult population (18-64 years) and 24% of VE against transmission, three months after the full vaccination for individuals aged 18 and above [118, 123].

In the absence of data about VE_{symp} and VE_{transm} in adolescents against the Delta variant when the Article #1 was carried out, we considered the maximal VE estimates found for adults (93% against symptomatic infection [118]; 50% against transmission [123]). This choice was informed by evidence supporting a more robust immune response among adolescents relative to adults [121]. Furthermore, since that vaccination in adolescents was launched later compared to that for adults, we considered an average delay of 2-3 months post-full vaccination for selecting the VE_{inf} . This parameter was set to 88% in line with [121]. For children, we relied on estimates from clinical trials [126], as vaccination for this group was approved in Europe in December 2021 and VE data were not available at the time

of Article #1 (see Section 1.4). Therefore, we considered 91% VE_{inf} for children [126], while VE_{symp} and VE_{transm} were set equal to those for adolescents. Table 2.5 presents instead the values used in the most recent publication, namely Article #2. In the article in preparation, Article #3, we revised the estimates of VE s in children and adults to include the rapid waning from the vaccine administration and a reduced protection against the Omicron variant [93, 94].

TABLE 2.5: Vaccine effectiveness (VE) against infection and transmission in children and teachers for the Omicron variant as in Article #2

Role	VE	Delay	Doses	Value	Source
Teachers	against infection	6 months	from 2 doses	15%	[124]
		within 4 weeks	from booster dose	70%	[124]
	against transmission			20%	assumed
Children	against infection	within 4 weeks	from 2 doses	50%	[125]
				20%	[125]
	against transmission			20%	assumed

2.4 Simulated school protocols

Symptom-based testing and case isolation were considered the basic strategies present in all protocols. In addition to this basic strategy, several intervention protocols were considered. The list of the simulated protocols is reported in Table 2.6. For testing and screening strategies, two different types of tests were considered: salivary PCR tests for primary schools and anterior nasal LFD tests for secondary schools. In all cases, teachers had to show a proven negative PCR test in order to return to school after infection (see Section 2.4.2 for test sensitivity). For each protocol, the number of cases was estimated either over the full period or at the peak, and the case reduction was evaluated with respect to symptom-based testing or reactive screening. According to the research questions behind each article, the following outputs were further considered: number of additional classes with active infection, increase in student-days lost, and number of tests per student.

2.4.1 Screening parameters

2.4.2 Test sensitivity

Two types of tests were considered in the simulations, in line with the tests adopted for the screening at the school in France. Specifically, RT-PCR tests were performed on saliva samples in primary schools, and anterior nasal antigen tests (lateral flow device, LFD) were administered in secondary schools.

Saliva RT-PCR

Evidence in the literature suggests that the performance of saliva samples is comparable to that of nasopharyngeal samples for symptomatic individuals [130, 131, 132, 133]. On

the contrary, for asymptomatic individuals, the sensitivity of saliva samples may be lower compared to that of nasopharyngeal samples during the convalescent phase [134]. The test sensitivity curve for symptomatic cases was derived from the interpolation of data from the onset of symptoms [135]. The peak of the fitted curve was 96%. For asymptomatic cases, data from RT-PCR saliva samples from asymptomatic cases (expressed in days since first matched positive viral culture) as reported in [136] were instead considered. Figure 2.10 shows the time-varying test sensitivity curves for the symptomatic and asymptomatic cases.

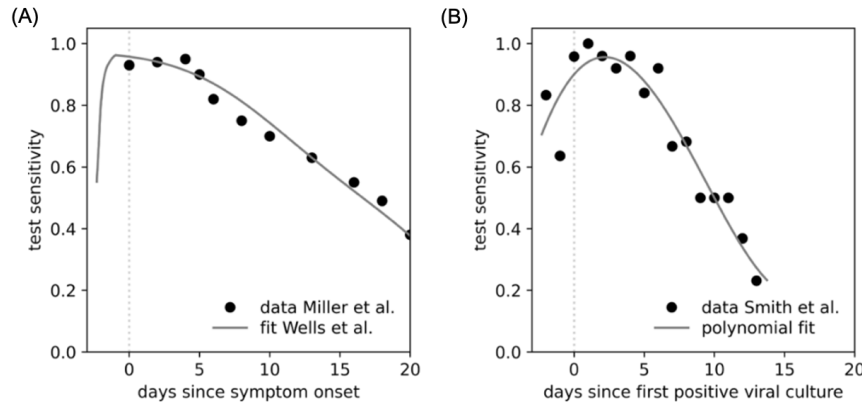


FIGURE 2.10: (A) Naso-pharyngeal samples from symptomatic cases, data from [135] and fit from [137]. (B) Saliva samples from asymptomatic cases. Data from [136] and polynomial fit of degree 4 minimizing the mean squared error.

Lateral Flow Device

The sensitivity of LFD tests has been shown to differ across symptomatic and asymptomatic cases, as well as across various age groups [138, 139, 140, 141]. To address the lack of time-dependent and age-stratified data, we assumed the same time dependence as in adults for the other age classes [136]. Then, we scaled the values to match the peak sensitivity estimates for symptomatic and asymptomatic cases in adults, adolescents, and children obtained from [142]. As the sensitivity of LFD tests was measured with respect to RT-PCR tests in the previous studies [136] [142], we adjusted the time-varying sensitivity of LFD tests to that of RT-PCR anterior nasal tests. We considered a peak sensitivity for the RT-PCR anterior nasal tests of 88% compared to RT-PCR nasopharyngeal sensitivity tests. This value corresponded to the upper bound of the estimate provided in [143]. After adjusting for RT-PCR tests, the absolute peak sensitivity of LFD tests for a symptomatic adult was found to be 81%, considering the peak sensitivity of RT-PCR nasopharyngeal tests as 96% [137]. The resulting time-varying test sensitivity curves are shown in Figure 2.11. Sensitivity analysis was conducted with the lower bound of 82% as in [143].

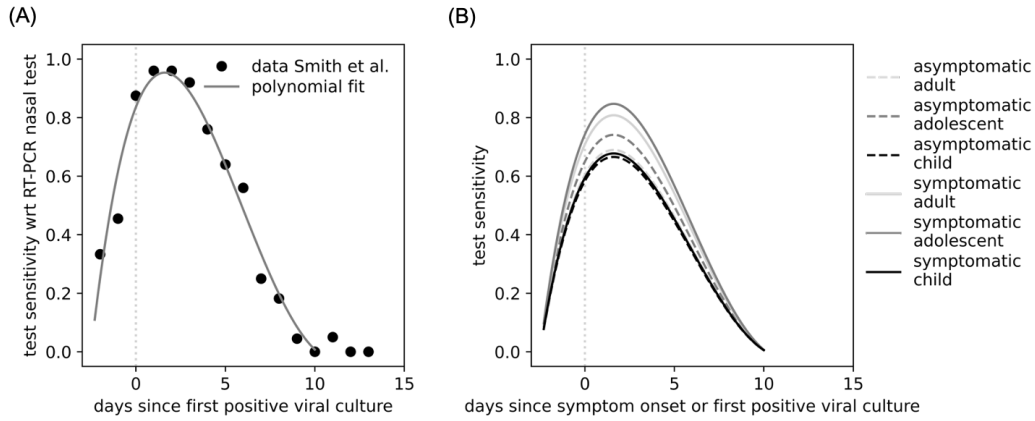


FIGURE 2.11: (A) Test sensitivity of PCR nasal tests from adult asymptomatic cases [136]. Data from [136] are fitted with a polynomial of degree 4 minimizing the mean squared error. (B) Absolute test sensitivity considering the sensitivity of the RT-PCR anterior nasal tests at 88% [143] and the sensitivity of the RT-PCR nasopharyngeal test at 96% [137]. The time dependence measured in [136] is adjusted to match the peak sensitivity values from [142] for symptomatic and asymptomatic cases in adults, adolescents, and children

2.5 Inference framework

The model was first fitted to the test results data of the pilot screening initiatives conducted in participating schools in the Ain, Loire, and Rhône departments in the Auvergne-Rhône-Alpes region during the spring 2021 wave, as introduced in Subsection 2.1.1. This methodological approach was then extended and adapted to the analysis conducted in Article #3 in which data coming from the experimental weekly screening regimen were used (see Subsection 2.1.1). In the following section, I describe the statistical framework developed for Article #1. Analogous considerations can be made for the other case with the necessary modifications.

2.5.1 Maximum likelihood estimates of the school transmission rate

I conducted multiple independent stochastic simulations in each department to simulate the spreading of the Alpha variant in schools, from week 08 to week 14 of 2021 with the symptomatic testing in place, coupled with the reactive closure of the class. The simulations were initialized with a certain number of infectious students and teachers based on data from [99]. Then, I adjusted the number of introductions over the school period, as explained in Section 2.3.2. An initial level of immunity was considered as well [144].

I fitted the model to the number of positive students ($n_{obs}(w, dep)$) detected in each department (dep) during weeks $w = 12, 13$, using screening data collected in weeks selected through the inclusion criterion (see Section 2.1.1). I used a Binomial distribution to represent the number of students testing positive among those who were tested. The likelihood function was defined as:

$$L(Data|\beta) = \prod_{dep=1}^3 \prod_{w=12}^{13} P_{Binomial}(n_{obs}(w, dep); preva_{pred}(w, dep), \beta)$$

where β was the unknown parameter to be estimated, P_{Binomial} was the probability mass function of a Binomial distribution, $\text{preva}_{\text{pred}}(w, \text{dep})$ was the prevalence predicted by the model under the corresponding school protocol at week w in department dep (correcting for test sensitivity), and w and dep were the weeks and the departments considered for the fit. The unknown parameter β was estimated at maximum likelihood using grid-based exploration and was considered to be non-dependent on the department (i.e., mandatory use of masks and protocols, as well as symptomatic testing paired with reactive class closure). The likelihood ratio was used to calculate the confidence intervals.

I extended the same approach to the analysis in Article #3. In this case, I also estimated two additional parameters, namely the detection rates p_{d1} and p_{d2} . The parameters p_{d1} and p_{d2} represented the community detection rates before and after the experimentation of the weekly screening regimen during the Delta wave (see Section 2.1.1). These parameters were estimated by exploring in a grid different possible combinations of values and then selecting the ones that, when combined with the transmission rate β , produced the best Akaike information criterion (AIC) (see Chapter 5).

2.5.2 Effective reproductive number

We simulated spreading for a given transmission rate β by testing every potential individual in each school as a seed under certain population conditions (e.g., natural immunity, vaccination) and school protocols. We defined the effective reproductive number as the ratio between the number of individuals infected in the second generation and the number of individuals infected in the first generation. For each school type, R_{school} was expressed as a function of the transmissibility β , by fitting the following relation to the results of the simulated outbreaks

$$R_{\text{school}} = a(1 - e^{-b\beta})$$

Estimates of the effective reproductive number in the primary and secondary schools during the spring 2021 wave in France from the maximum likelihood estimate of the transmissibility β are shown in Figure 2.12 as an example. In Article #1, these estimates were compared to the time-varying effective reproductive number R_t obtained from community surveillance data with the EpiEstim approach [145].

Once we had the transmission rate $\beta_{\text{Alpha}, \text{MLE}}$, we fitted the predicted offspring distribution to a negative binomial distribution to estimate the overdispersion parameter k . This allowed us to measure the variability in the outcomes, how they differ from the average, and therefore, understand the chance of having super spreading events or potential extinctions within schools.

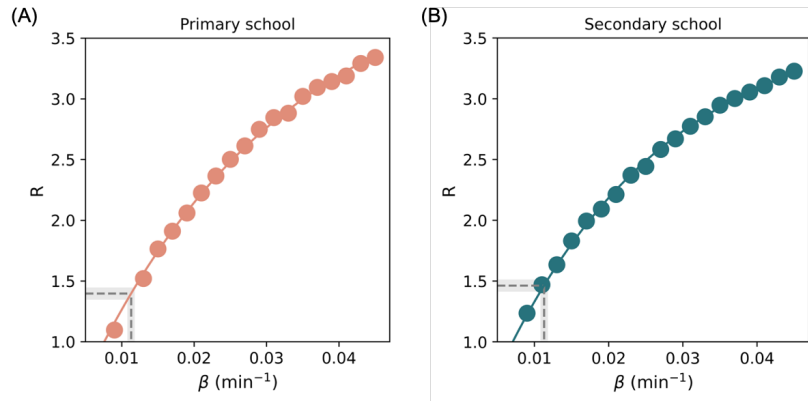


FIGURE 2.12: Effective reproductive number R_{school} in primary school (A) and in secondary school (B) as a function of the transmission per contact per unit time β under the conditions of the spring 2021 wave

2.6 Limitations

The methodological framework presented in this Chapter relies on empirical school networks and field data. In fact, student prevalence points are used to estimate transmissibility per contact at school, and observed adherence is used to inform simulated screening interventions. However, we acknowledge potential methodological limitations. In this section, I will discuss some of the main points.

First, the school networks used in the simulations were derived from a pre-pandemic period, while contact patterns during COVID-19 may have differed. Since we lacked data on contact reduction at school due to physical interventions, we used the interactions observed instead of assuming possible values. Further investigations would be useful to quantify this element and assess compliance with physical distancing.

In a later study [146], wearable devices were used to record close contacts among students from grades 1 to 12 between March 1 and 18, 2022, at Taizhou Minxing School, China [146]. These records included interpersonal distance, facial orientation, and relative position with finer spatial (1 m) and temporal (1/6 s) resolution compared to the contacts considered in this thesis. Similar to our networks, close contact rates were higher during breaks than during classes, with younger students usually having higher close contact rates. During breaks, face-to-face contact was found to be dominant, while face-to-back contact was the main orientation for close contact during classes. However, it is not clear from the article which distancing protocol was in place at school. Moreover, the very small sample size (24 students) and limited time collection (55 min) may be insufficient to characterize contact patterns. According to estimations derived from a survey in the UK, the contact rate at school among young children was reduced by 53% under strict physical distancing guidelines after school reopened following the first lockdown [147]. However, the contact data estimated by the survey in [147] were obtained right after the first lockdown, when between 30% and 40% of children had returned to school and the class sizes were greatly reduced in the UK. Consequently, it is reasonable to consider a lower reduction in contact rates with the full return to school [148] (Figure 2.13).

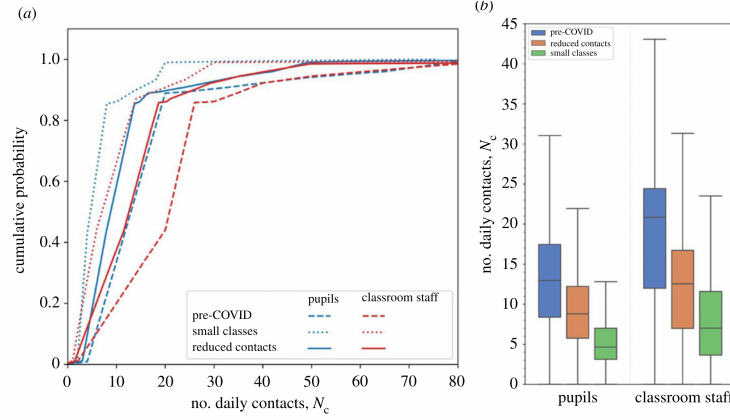


FIGURE 2.13: (A) Empirical cumulative distribution functions for the number of daily contacts in primary school classrooms derived from the Structured Expert Judgement Survey for pupils (blue) and classroom staff (teachers and teaching assistants; red) for pre-COVID times (dashed lines) and after school reopening in June–July 2020 (dotted lines). (B) Box and whisker plots (with outliers removed) comparing the number of daily contacts for pupils and classroom staff in pre-COVID times for small classes and modelled for full classes under conditions to reduce contacts Figure from [148]

Nevertheless, we modified the primary school network to simulate cohorting measures to include possible reductions in contacts. This was achieved by reducing the duration of contacts between classes, which we identified as our cohorts. Specifically, the duration of each contact occurring between individuals belonging to different classes was reduced, while contacts between those same individuals within their cohorts were reinforced by either creating a new contact or prolonging an existing one. The algorithm was designed to reproduce the fact that if students are unable to meet a friend in a different class (or cohort), they instead spend more time with a close friend in the same cohort. The results on the effect of cohorting are presented in a correlated publication [15] and in the Supplementary Information of Article #1 [6] and discussed in Chapter 3. Another possibility would be reducing contacts within classes, but very few countries in Europe have proposed cohorting within classes. France preferred to reduce contacts between classes where possible, similar to what was implemented in our version of cohorting. Other countries, such as Finland, Sweden, and Denmark, did not require any physical distancing in students [149]. Cohorting can indeed be hard to apply when spaces are limited, and it could be difficult to achieve for children. Therefore, it is still reasonable to consider that contacts may resemble those registered during the pre-pandemic period in most circumstances.

Different organizational structures can also affect contact patterns in schools. In the absence of contact data with a high temporal resolution like the one considered in this thesis, contact matrices can be used to describe interactions. We showed in a correlated work [16] that this type of data representation did not alter the identification of the most effective strategy and the rank of the protocols (from the most to the least effective) is preserved through them.

Second, the networks account only for contacts within schools. The estimate of the expected weekly number of imported cases was readapted from [101, 103]. Since data to quantify the underdetection rate in children were unavailable, we used an estimate from

the literature for the Alpha period in Article #1 [102]. The estimate could be considered reliable since symptomatic testing was still prioritized in the Alpha phase and no strong control measures were applied in schools that could allow for asymptomatic case identification in France. However, the detection rate could have changed in the following periods, especially after the wide diffusion of self-tests during the successive waves [150]. Unfortunately, the lack of a control case during the first round of the experimental weekly screening and the limited availability of data prevented the quantification of the detection rate in the Delta period. For this reason, we estimated the underdetection rate together with the transmission rate in the schools where the experimental weekly screening was applied during the Delta wave. On the other hand, the analysis of testing data from other countries where systematic screening was performed for a longer time and across variants, such as the canton of Basel in Switzerland, would provide a more precise estimate of the detection rate by comparison with others with less stringent measures.

Regarding the parameterization used, I assumed reduced susceptibility and transmissibility for children and adolescents, as preliminarily suggested by different studies discussed in Chapter 1. However, with the arrival of new variants, new evidence indicates a higher susceptibility and infectivity [28, 106]. To account for possible effects on transmission, sensitivity analyses were performed on these parameters. Moreover, for the Omicron variant, I modelled reinfection, assuming a combined effect between age-dependent susceptibility and a reduced infection probability given by a prior infection. Another possible approach would have been to consider only the highest one between them. However, evidence shows that hybrid immunity (i.e., vaccine plus past infection) is stronger than the protection provided by considering only one of the two events [151, 152].

Finally, the studies presented in the subsequent Chapters focus on the school setting and cannot directly quantify the impact that school protocols may have on community incidence. This was complicated, for instance, by the fact that no information on household composition or the number of infections in each family was collected during the experimental campaigns in France. In this case, studies on outbreak investigations and transmission chain reconstruction can provide more insights.

In conclusion, despite the acknowledged limitations, we have successfully developed an agent-based model using empirical records of contacts in schools. This model allowed us to simulate the transmission of SARS-CoV-2 through person-to-person interactions. By adopting an individual-level resolution, we were able to estimate the school effective reproductive number and its overdispersion, as well as measure the effectiveness of school interventions triggered by a single person and acting on contacts.

In the forthcoming Chapters, I will present the application of the model for the Alpha, Delta, and Omicron waves. The results aimed to enlarge the comprehension of COVID-19 dynamics within the school setting and add insights into the body of research focused on improving the safety of schools under pandemic conditions.

TABLE 2.6: Simulated testing and screening protocols

Protocols	Description	Article	Notes
Symptom-based testing	Suspected COVID-19 cases are tested and isolated until the test result is available. Confirmed positive cases are isolated for 7 days. In isolation, there are no school contacts.	#1, #2, #3	Basic strategy present in all simulated protocols
Reactive class closure	After the identification of a case through symptom-based testing, the class is closed and put into quarantine for 7 days. If quarantined individuals develop symptoms, they remain in isolation for 7 or 10 days before returning to school. During quarantine, there are no school contacts, but individuals can get the infection from community contacts.	#1, #2, #3	Largely adopted in France before the Delta wave in November 2021 and in Italy throughout the pandemic [127]
Reactive level closure	As above, except for the quarantine that is applied to the classes of the same level (two classes in the primary school) or specialization (three in the secondary school) as the detected case.	#1, #2, #3	Considered since empirical data showed a larger mixing between students of the same level or specialization than between students of different levels or specializations
Reactive screening of the class	<p>Screening of the entire class on the day after detection of the case by symptom-based testing, followed by a control screening on days 4 or 7 after case identification to detect undetected cases. Only positive individuals undergo isolation. In isolation, there are no school contacts. I assumed that 100% of the non-vaccinated school population adhered to the screening.</p> <p>As before, with control screening on days 7 after case identification. I assumed that 100% of the class population adheres to screening independently of vaccination.</p> <p>As before, with control screening on day 7 after case identification. I considered that 68% of the class population adheres to screening. Students not compliant with screening are isolated for 10 days.</p>	<p>#1</p> <p>#2</p> <p>#3</p>	<p>Adopted in France during the Delta wave to avoid class closure after being experimented in 10 departments [66, 128]</p>
Strengthened reactive screening of the class	Screening of the entire class on the day of the case detection by symptom-based testing, followed by a control screening on days 2 and 4 after case identification to detect undetected cases. Only negative individuals can continue in-person learning. During isolation, positive individuals can not have school contacts.	#2, #3	Adopted in France during the Omicron wave to avoid class closure [129]
Regular screening	<p>Screening of students and teachers with varying frequency. Adherence is distributed among non-vaccinated students and teachers. Only positive cases are isolated for 7 days.</p> <p>Adherence is distributed among all students and teachers regardless of the vaccination status.</p> <p>Adherence is distributed among students regardless the vaccination status.</p>	<p>#1</p> <p>#2</p> <p>#3</p>	<p>Regularly applied in Basel canton in Switzerland from March 2021 [54].</p> <p>Tested in France in selected primary schools.</p>
Regular testing and reactive closure of the class	As before, with additional class closure triggered at every detected case through screening.	#1	

TABLE 2.7: Screening parameters used to define detection and isolation in testing and screening protocols

Variable	Description	Value	Source	Sensitivity
p_d	probability of detection of COVID-19 infection among clinical cases	0.3 for primary students 0.5 in secondary students and teachers	[87, 88]	0.2, 0.5 0.4, 0.6
Δq	duration of isolation and reactive quarantine according to protocol and country under study	7, 10 days	informed by French and Italian Ministry of Education	–
W	weekly frequency of the regular screenings	0.5, 1, 2 per week in Article #1 1 and 2 per week in Article #2 1 per week in Article #3	assumed as in Basel canton and additional value as in the experimental weekly screening in France	– – –
f	adherence to regular screening	10%, 50%, 75%, 100% in Article #1 75% in Article #2 time-varying adherence in Article #3	informed from pilot screening plus additional values as in Basel canton informed from experimental weekly screening data	– – –
$f_{reactive}$	adherence to reactive class screening	100% in Article #1, #2 68% in Article #3	assumed informed from experimental weekly screening data	– –
$turn$	turnaround time	1 day for PCR test in Article #1, #2, #3 15 min for PCR in Article #1, #2, #3	assumed assumed	+12h in Article #2 –

School transmissibility during the Alpha outbreak and school protocols analysis to minimise educational disruption in a Delta scenario

In this Chapter, I will present the first modelling work I carried out covering the spring Alpha wave in France and a Delta scenario analysis. I provided estimates of the school-specific effective reproductive number in primary and secondary schools during the rising Alpha phase. I performed a cost effectiveness analysis of different testing protocols to guarantee in-person learning in a Delta scenario for the following winter 2021. The article reporting this research was published in *The Lancet Infectious Disease* journal [6].

3.1 Introduction

In the spring of 2020, schools worldwide were closed to slow down the spread of SARS-CoV-2. However, the fragmented knowledge about viral transmission in children posed challenges in safely maintaining in-person learning during the new academic year. While research suggested that children might be less susceptible to the infection and less infectious compared to adults (see Chapter 1), there were instances of viral transmission occurring in schools. Examples included outbreaks reported in a high school in Israel ten days after the resumption of lessons in May 2020 [153] and in a school camp in the USA in June 2020 [154].

In response to confirmed infections in students, governments sought ways to address the issue. Initial modelling studies tried to inform the debate on potential options for reopening schools in September 2020 after the first lockdown, proposing different test-trace-isolation options at the general population level [155, 156]. Within schools, the initial guidelines outlined by the European Centre for Disease Prevention and Control (ECDC) for the academic year starting in September 2020 included self-quarantine of class contacts to interrupt further transmission from primary symptomatic cases or confirmed cases in students [157]. However, this solution did not completely solve the problem of discontinuity in in-person education, leading to a shift to remote learning and the forced isolation of all students in the same class. Consequently, for the new academic year, a natural question arose about the existence of alternative school measures that could combine epidemic control with safe in-person learning while minimizing disruptions for students. To address the uncertainties

surrounding the transmission of SARS-CoV-2 in schools and the challenging task of choosing the most appropriate school strategy, my work aimed to achieve the following objectives:

- quantify the transmissibility in schools,
- estimate the effectiveness of testing strategies in reducing transmission while minimizing absences from schools.

The explored testing strategies ranged from symptomatic testing only to screening, which involved routine testing of the unvaccinated school population to identify active cases and prevent onward transmission. I fitted the agent-based transmission model described in Chapter 2 to the field data collected in France during the pilot screening campaign in Spring 2021. This allowed us to estimate the effective reproductive number associated with the Alpha variant period. Finally, I conducted a cost-benefit analysis by comparing the strategies in a prototypical primary and secondary school, anticipating a Delta scenario for the winter of 2021. Since March 2021, the Delta variant had emerged in the UK and had rapidly spread across Europe, becoming the dominant variant in the majority of the EU countries by July 2021 [158]. Since its emergence, the Delta variant had demonstrated a considerable transmission advantage over the Alpha variant [159], raising concerns about its potential impact on school activities. As expected, the Delta variant's properties led to a rapid circulation of the virus once children returned to school after the summer break, resulting in the suspension of school activities in France in September 2021. Just ten days after the start of the school calendar, 3,000 classes had already closed [160]. Therefore, extensive investigation into the role of schools in transmission was necessary to provide effective strategies. We did that by testing various *what if* scenarios.

For the analysis, different circumstances that could influence strategies (i.e. incoming flux of infected cases at school, R , and vaccination coverage) were considered. The main studied outcomes for primary and secondary schools were:

- case reduction,
- increase in student-days lost,

The baseline scenario involved symptom-based testing, against which improvements resulting from class or level closure and other testing strategies were gauged. Some of the results contained here were timely communicated to French authorities in April 2021 to emphasize the positive trade-off effects associated with regular screening [8], to the French Senate in June 2021 [10] to increase preparedness for the new academic year and, to the French National Authority for Health (Haute Autorité de Santé, HAS) to support the decision process for children vaccination in December 2021 [14].

3.2 Article #1: Screening and vaccination against COVID-19 to minimise school closure: a modelling study

Screening and vaccination against COVID-19 to minimise school closure: a modelling study

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Summary

Background Schools were closed extensively in 2020–21 to counter SARS-CoV-2 spread, impacting students' education and wellbeing. With highly contagious variants expanding in Europe, safe options to maintain schools open are urgently needed. By estimating school-specific transmissibility, our study evaluates costs and benefits of different protocols for SARS-CoV-2 control at school.

Methods We developed an agent-based model of SARS-CoV-2 transmission in schools. We used empirical contact data in a primary and a secondary school and data from pilot screenings in 683 schools during the alpha variant (B.1.1.7) wave in March–June, 2021, in France. We fitted the model to observed school prevalence to estimate the school-specific effective reproductive number for the alpha (R^{alpha}) and delta (B.1.617.2; R^{delta}) variants and performed a cost–benefit analysis examining different intervention protocols.

Findings We estimated R^{alpha} to be 1.40 (95% CI 1.35–1.45) in the primary school and 1.46 (1.41–1.51) in the secondary school during the spring wave, higher than the time-varying reproductive number estimated from community surveillance. Considering the delta variant and vaccination coverage in Europe as of mid-September, 2021, we estimated R^{delta} to be 1.66 (1.60–1.71) in primary schools and 1.10 (1.06–1.14) in secondary schools. Under these conditions, weekly testing of 75% of unvaccinated students (PCR tests on saliva samples in primary schools and lateral flow tests in secondary schools), in addition to symptom-based testing, would reduce cases by 34% (95% CI 32–36) in primary schools and 36% (35–39) in secondary schools compared with symptom-based testing alone. Insufficient adherence was recorded in pilot screening (median $\leq 53\%$). Regular testing would also reduce student-days lost up to 80% compared with reactive class closures. Moderate vaccination coverage in students would still benefit from regular testing for additional control—ie, weekly testing 75% of unvaccinated students would reduce cases compared with symptom-based testing only, by 23% in primary schools when 50% of children are vaccinated.

Interpretation The COVID-19 pandemic will probably continue to pose a risk to the safe and normal functioning of schools. Extending vaccination coverage in students, complemented by regular testing with good adherence, are essential steps to keep schools open when highly transmissible variants are circulating.

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Introduction

School closure has been extensively used worldwide against the COVID-19 pandemic. The first wave resulted in many countries going into strict lockdowns, closing schools for long periods of time,¹ and their reopening has been continuously challenged by successive waves and the need for physical-distancing restrictions. In Europe, depending on the country, students lost from 10 weeks to almost 50 weeks of school from March, 2020, to October, 2021, due to partial or total school closures (figure 1A). Strategies were affected by the limited understanding of viral circulation in children and their contribution to transmission.²

COVID-19 outbreaks in schools are difficult to document, as infections in children are mostly asymptomatic or present mild non-specific symptoms.³ Despite the lower susceptibility to infections in children than in adults,⁴

viral circulation can occur in school settings, especially in secondary schools.² Accumulating evidence is consistent with increased transmission in the community if schools are open,^{2,5} and model-based findings suggest that school closure might be used as an additional brake against the COVID-19 pandemic if other physical-distancing options are exhausted or undesired.^{6,7}

Keeping schools safely open remains a primary objective that goes beyond educational needs, affecting the social and mental development of children,⁸ as well as reducing inequality. Several countries implemented safety protocols at schools, including the use of facemasks, hand hygiene, and staggered arrival and breaks. Regular testing^{9–12} was introduced in a few countries as an additional control measure. Vaccination was extended to the population aged 5 years and older in Europe, yet it was reported to have

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Research in context

Evidence before this study

We searched PubMed, medRxiv, bioRxiv, and arXiv for articles in English published up to Dec 3, 2021, which had, in the title or abstract, the terms “COVID-19”, “testing”, and “schools”.

We found a total of 271 unique articles. 57 works were modelling papers on the spread of COVID-19, and of these 31 (54%) implemented agent-based models. However, very few integrated information from empirical contacts or considered the cost of school closures in terms of school-days lost by students. No study addressed the role of vaccination in children in the school setting or the interplay of adherence to screening with frequency of screening. Modelling studies reached a consensus on the fact that test turnaround time is more important than test sensitivity for efficient testing strategies.

Added value of this study

Governments around the world proposed school closures as a first measure to slow down viral spread; however, the need to safely keep schools open is arguably a primary objective for educational, mental health, and socioeconomic reasons. Using empirical contact data collected in a primary school and a secondary school and data on test results collected in pilot screenings during the 2021 spring wave of the alpha variant in France, we estimated the effective reproductive number specific to each school setting in that period and showed that transmission was higher in schools than in the community.

Accounting for the transmission advantage of the delta variant and vaccination coverage in Europe as of mid-September, 2021, we showed the need for regularly testing a partly immunised school population to reduce the number of cases while limiting the number of student-days lost. In particular, we highlighted the importance of adherence to screening, showing that higher screening frequency is needed to compensate for lower adherence. Model estimates indicate that the low levels of adherence recorded in pilot screenings during the third wave would be insufficient to control viral circulation in the school population. Increasing vaccination coverage in teachers did not impact potential outbreaks, mainly due to the large mixing among students. Regular testing would still provide a key benefit in decreasing viral circulation in a moderately vaccinated student population, or under waned protection against infection, and it would be especially important under the high-incidence conditions observed in the omicron wave.

Implications of all the available evidence

By studying different epidemic contexts and vaccination conditions, we provided a range of alternatives to school closure, to be implemented according to the epidemic activity and the reported adherence. These strategies become particularly important as the safety and normal functioning of classrooms are threatened by high community transmission rates. These results can inform national education systems to safely keep schools open while avoiding unnecessary closures.

progressed slowly in the majority of countries as of January, 2022.¹³ School protocols were challenged by the rapid surge of cases due to the delta (B.1.617.2) and omicron (B.1.1.529) variants in the 2021–22 winter season in Europe,¹⁴ threatening classroom safety. Assessing vaccination and protocols in schools is therefore key to maintaining schools open in light of a continuously evolving pandemic. Here, through an agent-based transmission model parameterised on empirical contacts at schools and fitted to field screening data in schools, we estimated the school-specific effective reproductive number (R) of SARS-CoV-2. We then evaluated intervention protocols combining school closures and screening, under varying immunity profiles of the school population, and accounting for age-specific differences in susceptibility to infection, contagiousness, contact patterns, and vaccine effectiveness.

Findings from this work informed the recommendations of the French National Immunisation Technical Advisory Group (Haute Autorité de Santé) on vaccination of children in December, 2021.

Methods

Empirical patterns of contacts

We used empirical data describing time-resolved, face-to-face proximity contacts between individuals in two educational settings, collected in France using

wearable radio frequency identification (RFID) sensors before the pandemic. The primary school dataset describes contacts among 232 students (aged 6–11 years) and ten teachers in a primary school in Lyon in October, 2009; the primary school was composed of five grades, each containing two classes.¹⁵ The secondary school dataset describes contacts among 325 students (aged 17–18 years) of nine classes in a secondary school in Marseille in December, 2013.¹⁶ Classes in the secondary school belonged to the second year of classes préparatoires, which is specific to the French schooling system for preparing students for University entry, and were divided into three groups based on the specialisation (mathematics and physics; physics, chemistry, and engineering studies; and biology).

We built temporal contact networks, composed of nodes representing individuals (classified by class and student or teacher) and links representing empirically measured proximity contacts occurring at a given time (appendix p 14). As each dataset covers only a few days, we developed an approach to temporally extend the datasets by generating synthetic networks of contacts that reproduce the main features observed empirically (class structure, within-class vs between-class links, contact duration heterogeneity, and similarity across days; appendix pp 14–18). The secondary school synthetic network was further extended to generate a synthetic first year (to consider the full curriculum of the classes

See Online for appendix

préparatoires), including teachers whose contacts were inferred from an additional dataset for the same school. The resulting network for the secondary school was composed of 650 students and 18 teachers.

Field screening data in schools during the spring, 2021, wave in France

In response to a rising third wave of SARS-CoV-2 in France in March, 2021, due to the alpha variant (B.1.1.7), local authorities in the Auvergne-Rhône-Alpes region proposed pilot screenings at schools on a voluntary basis to detect cases. We used data on adherence to screening and test results collected in 683 schools between March 8 and June 7, 2021 (weeks 10–23), in the Ain, Loire, and Rhône departments of the region (figure 1E). Screening was interrupted in April due to reactive school closure (week 14) and the Easter holidays (weeks 15–16) while the country underwent the third national lockdown; it was resumed in week 17 at school reopening (week 18 for secondary schools; figure 1G). Screenings involved 94 pre-schools (ages 3–5 years), 427 primary schools (ages 6–11 years), 158 middle schools (ages 12–15 years), and four high schools (ages 16–18 years), for a total of 209 564 students and 18 019 staff and teachers tested. PCR tests on saliva samples were proposed in pre-schools and primary schools and anterior nasal lateral flow device (LFD) tests in middle and high schools. More details on the number of participating schools by department and over time, and on the observed adherence to testing, are provided in the appendix (pp 19–22).

Ethics statement

Contact studies were approved by the Commission Nationale de l'Informatique et des Libertés (the French national body responsible for ethics and privacy; 1719527 and 1427054) and school authorities. Informed consent was obtained from participants or their parents if they were minors (age <18 years). No personal information of participants was associated with the RFID identifier. Testing at school was part of surveillance activities approved by school authorities and proposed with parental consent. Screening data were provided in aggregated and anonymised form.

Transmission modelling

We developed a stochastic agent-based model of SARS-CoV-2 transmission on the network of contacts. Infection progression includes prodromic transmission, followed by clinical or subclinical disease stages, informed from empirical distributions. Transmission occurs with a given transmissibility (β) per contact per unit time between an infectious individual and a susceptible one. β was inferred by fitting the model to data from screening results during the 2021 spring wave. Individuals in the asymptomatic compartments were considered less infectious than individuals in the symptomatic

compartments and to remain undocumented unless tested;¹⁷ a sensitivity analysis was performed on the value of the reduced transmissibility in the asymptomatic stage.

The model was parameterised with age-specific estimates of susceptibility, transmissibility, probability of developing symptoms, and probability to detect a case based on symptoms (appendix pp 4–6). A systematic review⁴ indicated that children (younger than 10–14 years) have lower susceptibility to SARS-CoV-2 than adults, but building evidence suggests that adolescents (older than 10–12 years) might be as susceptible as adults (≥ 20 years).^{4,18} Here, we considered a relative susceptibility of 50% in primary school children and 75% in secondary school adolescents compared with adults for the main analysis and 100% susceptibility in adolescents in a sensitivity analysis. The probability of recognising a suspected SARS-CoV-2 infection from symptoms was set to 30% for children and 50% for adolescents and adults on the basis of studies indicating that about two-thirds of symptomatic children³ and half of symptomatic adults¹⁹ have unrecognised symptoms before diagnosis. These values were varied in sensitivity analyses (appendix pp 9, 51). We considered a relative transmissibility of 63% in children compared with adults as evidence suggests that transmission in children might be less efficient than in adults,²⁰ and we tested 80% relative transmissibility in a sensitivity analysis.

The model was further stratified to account for vaccination status and to include vaccine effectiveness against infection, transmission, and clinical symptoms given infection²¹ (appendix pp 9–12). Higher and lower values for vaccine effectiveness were tested in sensitivity analyses. Full details on the transmission model are reported in the appendix (pp 4–13).

Closure and screening protocols

Symptom-based testing and case isolation was considered the basic strategy, present in all protocols, and against which interventions were evaluated. Under the basic strategy, confirmed cases isolate for 7 days. In addition to the basic strategy, we considered several intervention protocols. First, we considered a protocol of reactive quarantine of the class, wherein once a case is identified through symptom-based testing their class is closed and put into quarantine for 7 days. If quarantined individuals develop symptoms, they remain in isolation for an additional 7 days before returning to school. This protocol was largely adopted in France before the delta wave in November, 2021. The second protocol was reactive quarantine of the class level or specialisation, which is similar to the reactive quarantine of the class protocol except that quarantine is applied to the classes of the same level (two classes in the primary school) or specialisation (three in the secondary school) of the detected case. This option was considered as empirical data showed a larger mixing between students of the

same level or specialisation than between students of different levels or specialisations.^{15,16} Third, we considered reactive screening of the entire class on the day after detection of the case by symptom-based testing, followed by a control screening on days 4 or 7 after case identification to detect previously undetected cases. This protocol assumes that 100% of the non-vaccinated school population adheres to screening. This protocol was adopted in France during the delta wave. Fourth, we considered regular testing of the entire school once every 2 weeks or once or twice a week, in addition to symptom-based testing, with adherence among the non-vaccinated informed by field data and further explored in a range between 10% and 100%. Finally, we considered a protocol of regular testing with different levels of adherence among the non-vaccinated and reactive closure of the class triggered at every detected case.

Following protocols adopted in France, we assumed testing consisted of PCR tests on saliva samples for primary schools and anterior nasal LFD tests for secondary schools, with time-varying test sensitivity specific to each test and results available after 24 h for PCR and after 15 min for LFD tests (appendix pp 7–8). Teachers are required to show proof of a negative PCR test when returning to school after infection.

Inference framework

We used data on test results collected in the pilot screenings during the 2021 spring wave in the Ain, Loire, and Rhône departments to estimate the transmissibility per contact per unit time of the alpha variant (β^{alpha}) and the corresponding school-specific R for the alpha variant (R^{alpha}) in that period. The model was fitted to the observed prevalence of cases in students in the tested schools through a maximum likelihood approach. We used data from screenings performed during the rise of the spring wave (March 8 to April 2, 2021) that involved at least five schools and 500 screened students per week per department for each school type (primary or secondary) and with reported adherence to screening of at least 50% (reference inclusion criteria). In sensitivity analyses, we relaxed the constraint on adherence (sensitivity inclusion criteria). Simulations for the fit covered the period from week 8 (starting Feb 22, 2021, at school reopening after winter holidays) to week 13 (ending April 4) before the reactive school closure, and they were initialised with age-specific seroprevalence estimates.²² Weekly introductions at school were modelled stochastically, inferred from age-specific community surveillance data, and adjusted to account for detection rate and within-school transmission.²³ We computed R in each school as the ratio of the number of individuals infected at the second generation to the number infected at the first generation for each initial seed over 5000 simulated outbreaks. The estimated R refers to the reactive quarantine of the class protocol with a facemask

mandate applied in that period. Full details on the procedure are reported in the appendix (pp 23–29).

Analysis of school protocols in a delta winter wave scenario in Europe

To evaluate the efficacy of intervention protocols, we considered a 2021–22 winter scenario due to the delta variant, initialised with 25% natural immunity in the population, 60% of teachers vaccinated, and 40% of adolescents vaccinated, corresponding to the median vaccination coverage registered in countries in Europe by mid-September, 2021 (appendix p 31). The transmissibility per contact per unit time for the delta variant (β^{delta}) was estimated from the maximum likelihood estimate $\beta_{\text{MLE}} = \beta^{\text{alpha}}$, accounting for the transmissibility advantage of the delta variant.²⁴ The corresponding school-specific R for the delta variant (R^{delta}) was estimated from simulated outbreaks under the above immunity conditions, and considering the reactive quarantine of the class protocol with facemasks mandated. We additionally explored a range of R^{delta} values to account for the uncertainty in the estimate of delta transmissibility,²⁴ seasonal effects,²⁵ and variations in β_{MLE} due to the inclusion criteria considered in the inference. We considered low, moderate, sustained, and high weekly introductions modelled stochastically and corresponding to community surveillance incidence in primary school students ranging in time from 25 to more than 600 cases per 100 000 (low introductions), from 50 to 900 cases per 100 000 (moderate), from 100 to 1300 cases per 100 000 (sustained), and from 200 to 1800 cases per 100 000 (high); values for the secondary school are reported in the appendix (p 33).

To assess the efficacy of screening protocols under different immunity conditions, we explored a full range

Figure 1: School closure in Europe, empirical contact network features, and field screening data in schools in France

(A) Number of in-presence weeks lost by students in European countries because of school closures due to the pandemic. (B) Daily mean number of distinct contacts per individual within the class or between classes; horizontal dashed lines represent the mean class size, which was 23.2 students (SD 1.4) in the primary school and 35.8 (4.1) in the secondary school. (C) Daily mean time that an individual spends in interaction with contacts within the class or in other classes. (D) Daily mean time that a teacher or student spends in interaction with contacts. In panels B–D, histogram bars refer to the empirical networks, and points and error bars (with 95% bootstrap CIs) refer to the synthetic networks. In panels B and C, the increase in average number of contacts and duration in the synthetic secondary school networks compared with their empirical counterparts is due to the ad-hoc addition of contacts between school years. In panel D, no empirical data is shown for teachers in secondary schools as they did not participate in the data collection and their contact behaviour was inferred from another dataset (appendix p 15). (E) Number of schools participating in the pilot screenings during the spring 2021 wave in the Ain, Loire, and Rhône departments. (F) Observed adherence to screening; boxplots represent the median (middle line), IQR (box limits), and 2.5th and 97.5th percentiles (whiskers). (G) Number of schools participating in the pilot screenings and weekly incidence (dotted line) over time from community surveillance in the Ain, Loire, and Rhône departments during the 2021 spring wave; the vertical shaded areas indicate the school closures.

of vaccination coverage in children, adolescents, and teachers.

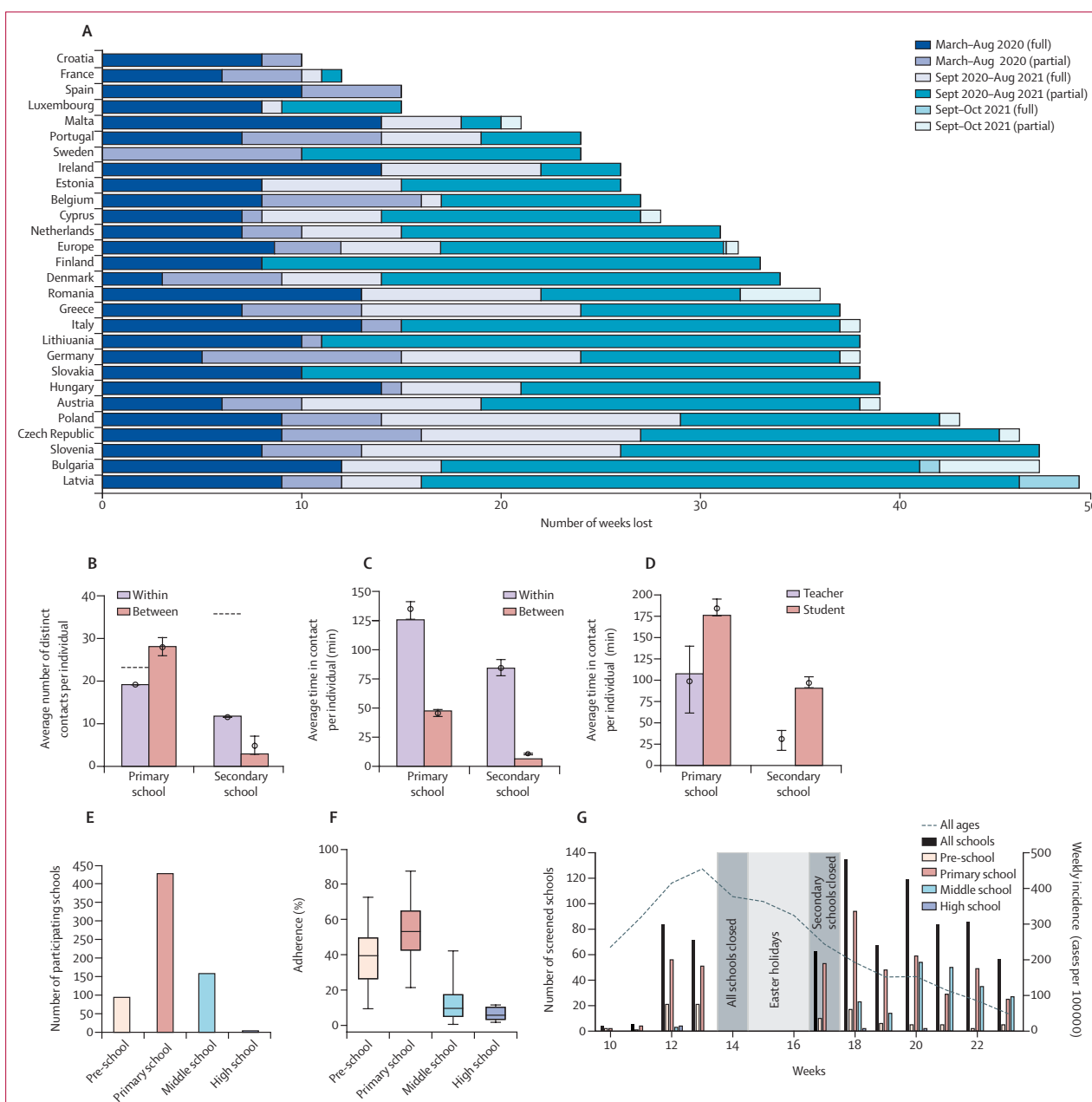
Analysis of school protocols in an omicron winter wave scenario in Europe

We considered the circulation of the highly transmissible and immune-evasive omicron variant that became dominant in Europe by the start of 2022.¹⁴ We tested the

efficacy of school protocols under the high-incidence conditions registered in France by mid-January, 2022 (5500 cases per 100 000 children aged 6–10 years). Details of this analysis are reported in the appendix (p 37).

Simulation details and analysis

Estimates for β and R were obtained from 5000 simulated stochastic outbreaks for each parameter set. Estimates



for R were compared with the age-specific, time-varying reproductive number (R_t), estimated from community surveillance data, with a one-sample t-test. We fitted the predicted offspring distribution to a negative binomial to estimate the overdispersion parameter k .²⁶ In the analysis of closure and screening protocols, we performed 1000 stochastic runs for the primary school and 2000 for the secondary school for each parameter set, over the course of a trimester (90 days). We computed medians and 95% bootstrap CIs from simulation outputs to compare protocols with a Mood's median test. IQRs were used to describe observed adherence. Network statistics in the primary and secondary schools were compared with a Student's t-test. We used R software version 4.1.1 for the statistical analyses.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Contact networks measured through wearable sensors displayed a strong community structure around the classes, common to both the primary and secondary schools (appendix p 14). The patterns of interaction, however, varied substantially between the two settings. On average, children had a larger number of distinct contacts during a day than adolescents, interacting with almost their entire class (83% vs 33% of the class, Student's t-test $p < 0.0001$; figure 1B). Approximately 50% more links occurred between classes than within classes in the primary school (28 vs 19 links, $p < 0.0001$), whereas in adolescents, 75% fewer links occurred between than within classes (three vs 12 links, $p < 0.0001$). After accounting for duration, students in both settings spent on average more time interacting within the class than outside the class ($p < 0.0001$; figure 1C) and established longer contacts than teachers (64% longer, $p = 0.009$; figure 1D).

Using the empirical contact patterns, we inferred the school-specific transmissibility from screening data in primary schools that satisfied the inclusion criteria: 71 primary schools with 12 146 tested students met the reference inclusion criteria, and 103 primary schools with 15 916 tested students met the sensitivity inclusion criteria. Secondary schools were excluded because of limited participation, but with β_{MLE} we could estimate the within-school R^{alpha} both in the primary school and in the secondary school. We estimated that R^{alpha} during the 2021 spring wave of the alpha variant in France when reactive class closures and facemask mandates were in place was 1.40 (95% CI 1.35–1.45) in primary schools that met the reference inclusion criteria, 1.44 (1.40–1.48) in primary schools that met the sensitivity inclusion criteria, 1.46 (1.41–1.51) in secondary schools that met the reference inclusion criteria, and 1.50 (1.46–1.54) in

secondary schools that met the sensitivity inclusion criteria (figure 2A). Estimates were higher than the R_t obtained from age-specific community surveillance in the same period (one-sample t-test $p < 0.0001$ in the primary and secondary school; figure 2C). We quantified a large individual-level variation in SARS-CoV-2 transmission in both schools, corresponding to an estimated overdispersion parameter k of 0.56 (95% CI 0.49–0.63) in the primary school and 0.52 (0.46–0.58) in the secondary school (figure 2B). Accounting for the transmissibility advantage of the delta variant and vaccination coverage in Europe, we estimated a school-specific R^{delta} of 1.66 (95% CI 1.60–1.71) for primary schools that met the reference inclusion criteria, 1.70 (1.66–1.75) for primary schools that met the sensitivity inclusion criteria, 1.10 (1.06–1.14) for secondary schools that met the reference inclusion criteria, and 1.13 (1.10–1.16) in secondary schools that met the sensitivity inclusion criteria. In the analysis of closure and screening protocols, we used the R^{delta} estimate obtained with the reference inclusion criteria, and explored ranges for R^{delta} of 1.46–2.00 in primary schools and 0.97–1.34 in secondary schools to account for the uncertainty associated with delta transmissibility, seasonal effects, and sensitivity inclusion criteria.

Under the estimated delta transmissibility and with sustained introductions, regular testing constitutes an efficient protocol for preventing infections in a partially immunised school population (figure 3A). If adherence among the non-vaccinated is large enough, regular testing can substantially outperform protocols based on simply identifying cases given recognisable symptoms and additionally closing or screening the class of the detected case (even with a follow-up control screening). However, screenings at schools during the 2021 spring wave in France were met with low or moderate participation rates. Adherence was higher in lower school levels (39% [IQR 26–49] in pre-school and 53% [43–65] in primary school) than in secondary schools (10% [5–17] in middle school and 6% [3–10] in high school; Mood's median test $p < 0.0001$; figure 1F). We found that with 50% adherence among the non-vaccinated—ie, approximately the value recorded in the French primary schools—weekly screening would reduce the number of cases by 21% (95% CI 19–23) in primary schools and 26% (24–28) in secondary schools compared with symptom-based testing alone. Case reduction would rise to 34% (32–36) and 36% (35–39) in primary and secondary schools, respectively, with 75% adherence. Alternatively, similar reductions would be achieved with 50% adherence and twice-weekly testing. These data show how infection prevention improves with both adherence and frequency of tests, and higher frequency is needed to compensate for lower adherence. However, if adherence to regular testing is too low (10%), as recorded in the French secondary schools, weekly testing would have little impact (<10% case reduction, similar to reactive screening and

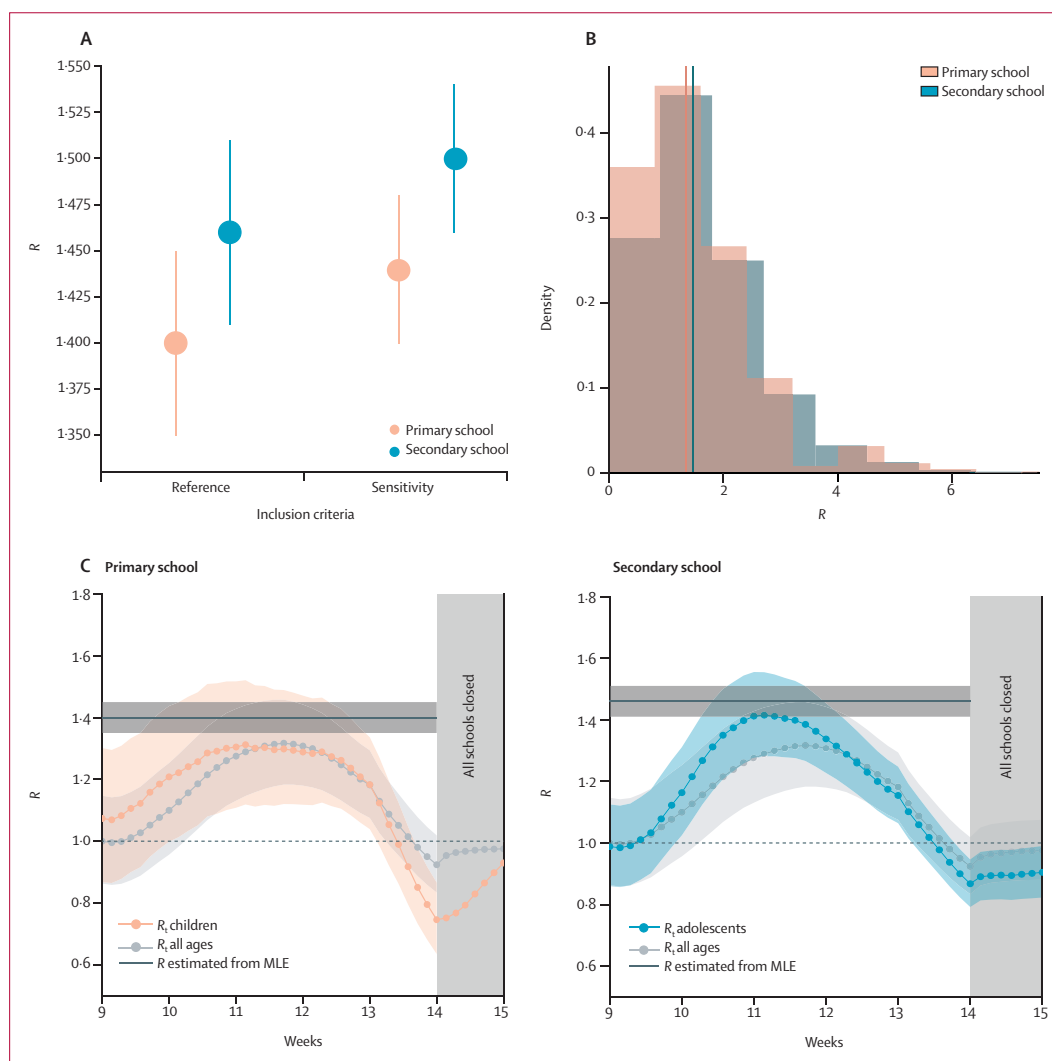


Figure 2: Estimates of R in the school setting during the 2021 spring wave in France due to the alpha variant

(A) Estimates of R in primary and secondary schools obtained with the reference and the sensitivity inclusion criteria by fitting the model to pilot screening data; estimates refer to the alpha variant during the 2021 spring wave in France, when reactive closure of classes and facemask mandates were in place, and error bars indicate 95% CIs. (B) Predicted offspring distribution in primary and secondary schools; bold vertical lines indicate R (ie, the average of the distribution) obtained with the reference inclusion criteria. (C) Comparison between the estimate of R for the alpha variant (bold horizontal line; the shaded area corresponds to its 95% CI) and R_t estimated from community surveillance in the Ain, Loire, and Rhône departments during the rise of the 2021 spring wave for primary schools and secondary schools. MLE=maximum likelihood estimate. R =effective reproductive number. R_t =time-varying reproductive number.

lower than reactive closure). Although trends are similar across settings, partial vaccination coverage in adolescents leads to smaller epidemic sizes in the secondary school than in the primary school (relative to the school size; figure 3B; appendix p 41).

As well as reducing the number of infections, regular testing is predicted to strongly limit the number of days of absence of students. Quarantine of the class leads to 17.7 (95% CI 17.4–17.9) and 32.6 (31.9–33.5) times more student-days lost in primary

and secondary schools, respectively, than when symptom-based testing is used alone (figure 4A). Days lost inevitably increase when reactive closure is extended to classes of the same level or specialisation. Not being sufficiently targeted, reactive closure quarantines individuals while their risk of infection might be low, and the virus might have spread to other classes (figure 3C). Reducing mixing across classes through cohorting improves control (appendix p 44). Despite detecting more cases, regular testing leads to a small

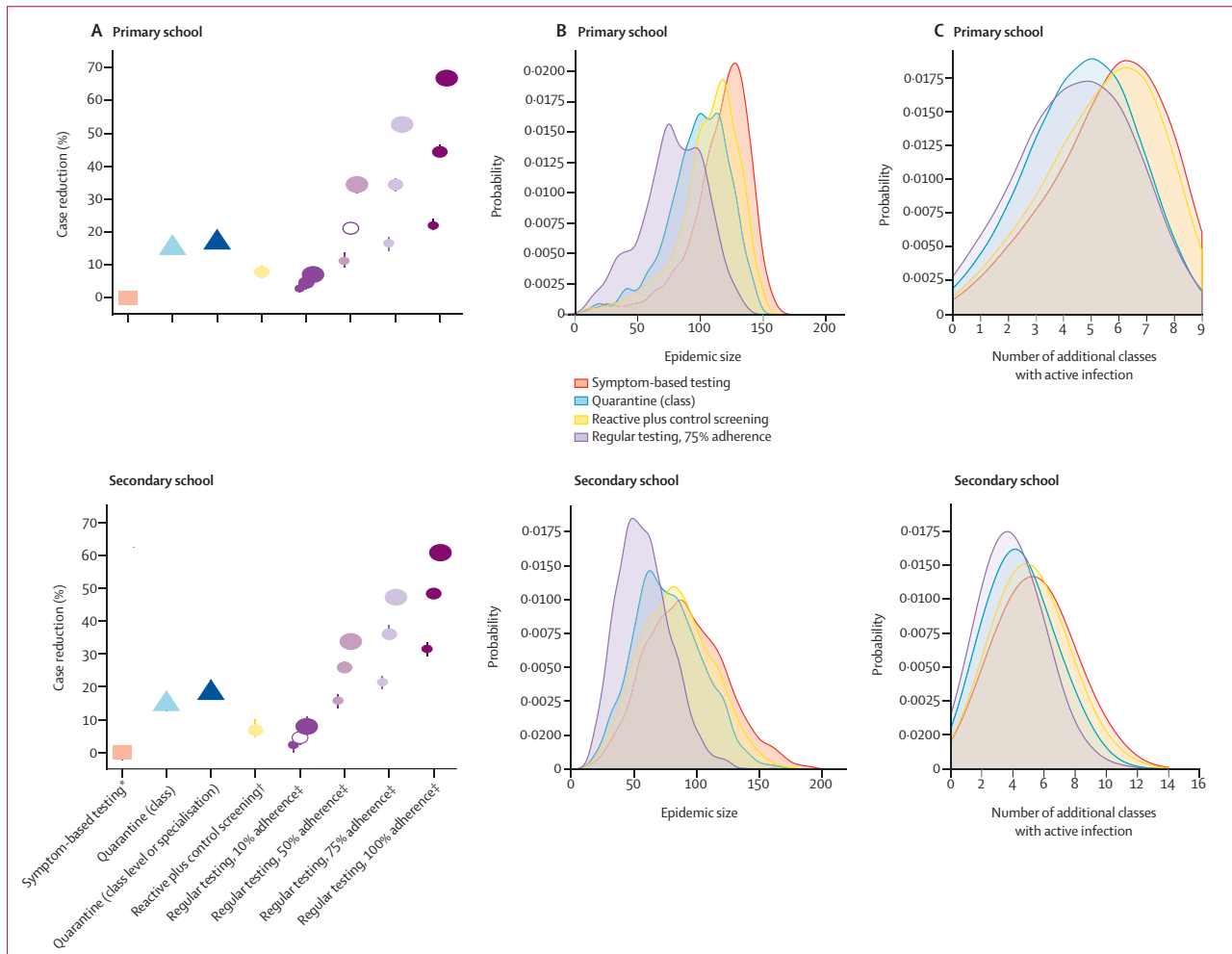


Figure 3: Efficiency of regular testing in educational environments

(A) Predicted case reduction relative to symptom-based testing alone in primary schools and secondary schools; the reduction is computed on the final epidemic size over 90 days. Error bars correspond to 95% bootstrap CIs (in some cases smaller than the symbol size). The empty marker corresponds to the adherence estimated from empirical data. (B) Probability distribution of the simulated epidemic size over 90 days in the primary school and secondary school for selected protocols (regular testing is performed weekly). (C) Probability distribution of the additional number of classes in the primary school and secondary school with at least one active infection when a case is confirmed, for selected protocols (regular testing is performed weekly). In all panels, simulations are parameterised with sustained introductions and the estimated effective reproductive number for the delta variant when reactive class closures and facemask mandates are in place, and accounting for differences in vaccination coverage. *All protocols involve symptom-based testing. †Reactive screening of the class is done on the day after detection of the case, followed by a control screening on day 4 after case identification, with 100% adherence among the non-vaccinated. ‡Regular testing is performed with one test every 1 week (medium-sized circle) or 2 weeks (smallest circle) or two tests per week (largest circle).

increase in student-days lost, less than 6.6 (6.4–6.8) times the number of days lost with the basic strategy and about 63–80% less than reactive class closure as isolation is applied only to detected cases. The cost-benefit analysis shows that for all regular testing strategies, the cost expressed as student-days lost remains low, even when the benefit becomes high, for a range of different epidemic conditions (figure 4B). Strategies based on class closures do not reach substantial benefit, even at large costs. Reactive screening limits days lost but with a negligible impact on viral

circulation. Closing the class at each case detected by regular testing improves case reduction but at the cost of increased absence from school (appendix p 43). Findings were robust to changes in detection rates and test sensitivity (appendix pp 51–52).

Higher incidence in the community (increasing the expected introductions at school) and larger values for R (increasing within-school transmission) reduce the benefit of weekly testing in primary schools, thus requiring increased adherence or frequency (figure 4C,D). The impact of introductions is milder in the secondary

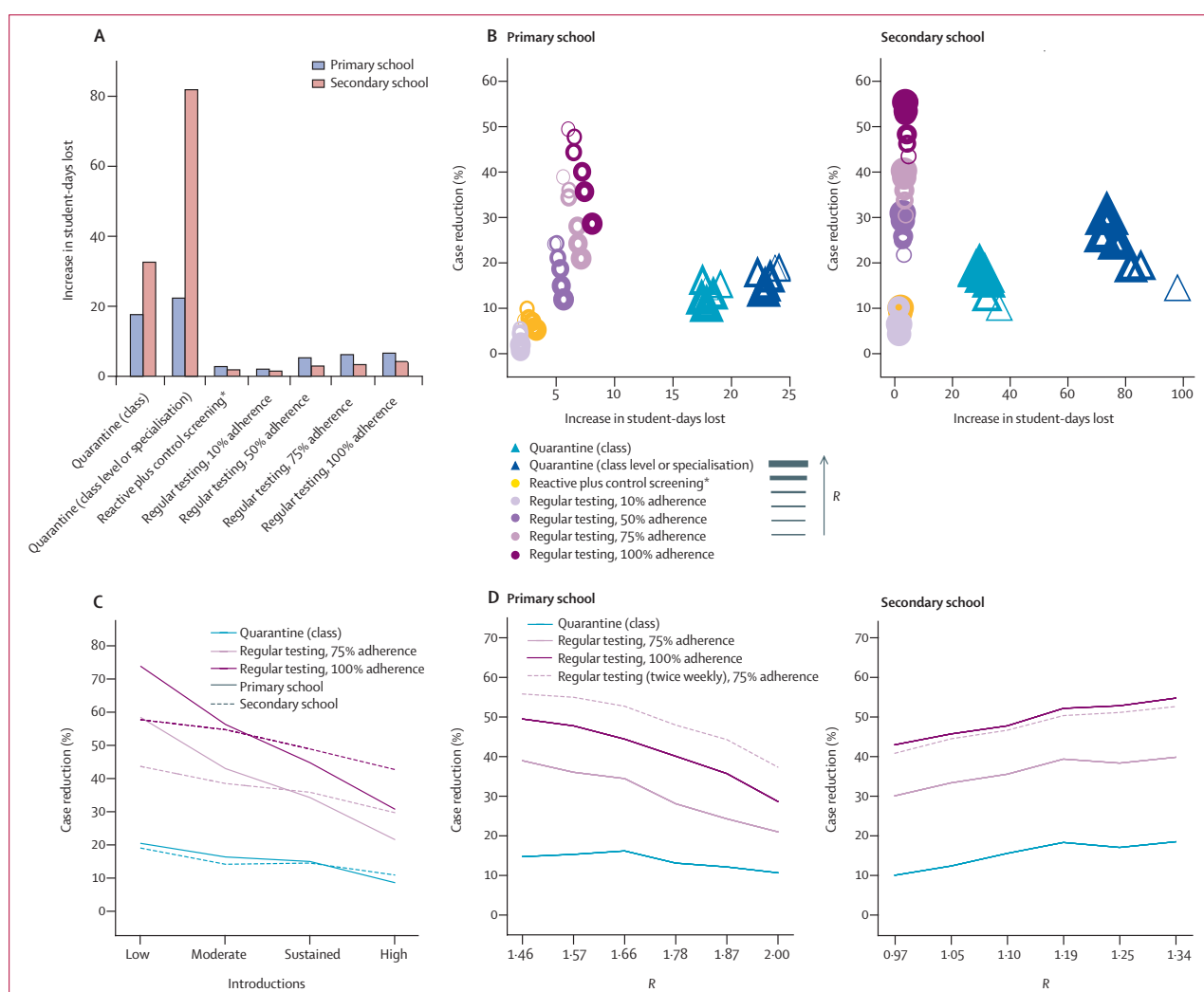


Figure 4: Cost-benefit analysis of regular testing in educational environments and the impact of introductions and R

(A) Predicted increase in student-days lost relative to symptom-based testing alone. Regular testing is performed weekly. Simulations are parameterised with sustained introductions and the estimated R^{eff} when reactive class closures and facemask mandates are in place, accounting for differences in vaccination coverage. (B) Predicted case reduction versus predicted increase in student-days lost in the primary school (R 1.46–2.00) and secondary school (R 0.97–1.34) for each protocol relative to symptom-based testing only. Regular testing is performed weekly. Simulations are parameterised with sustained introductions. (C) Predicted case reduction relative to symptom-based testing only for selected protocols (regular testing is performed weekly) as a function of the level of introductions; simulations are parameterised with the estimated R^{eff} . (D) Predicted case reduction relative to symptom-based testing alone for selected protocols in the primary school and secondary school as a function of R . Regular testing involves weekly screening unless otherwise indicated. Simulations are parameterised with sustained introductions. All protocols involve symptom-based testing. R =effective reproductive number. R^{eff} =effective reproductive number for the delta variant. *Reactive screening of the class is done on the day after detection of the case, followed by a control screening on day 4 after case identification, with 100% adherence among the non-vaccinated.

school than in the primary school due to vaccination of adolescents (figure 4D). Moreover, increasing R in this setting would increase the benefit of regular testing, contrary to the primary school case. This is due to a bell-shaped dependence of the infection prevention capacity of regular testing versus R (appendix p 46): in low-transmission conditions, only a few cases are present even under the scenario of symptom-based testing and case isolation, so that additional protocols yield marginal

benefit; as transmission increases from small values (the secondary school case, where R is small thanks to vaccination), efficiency increases. In high-transmission conditions, case prevention is hindered by too many infections generated between successive screenings, and efficiency decreases as transmission increases (the primary school case, with high R because of unvaccinated children). Changes in epidemiological parameters (transmissibility and susceptibility) yield changes in R

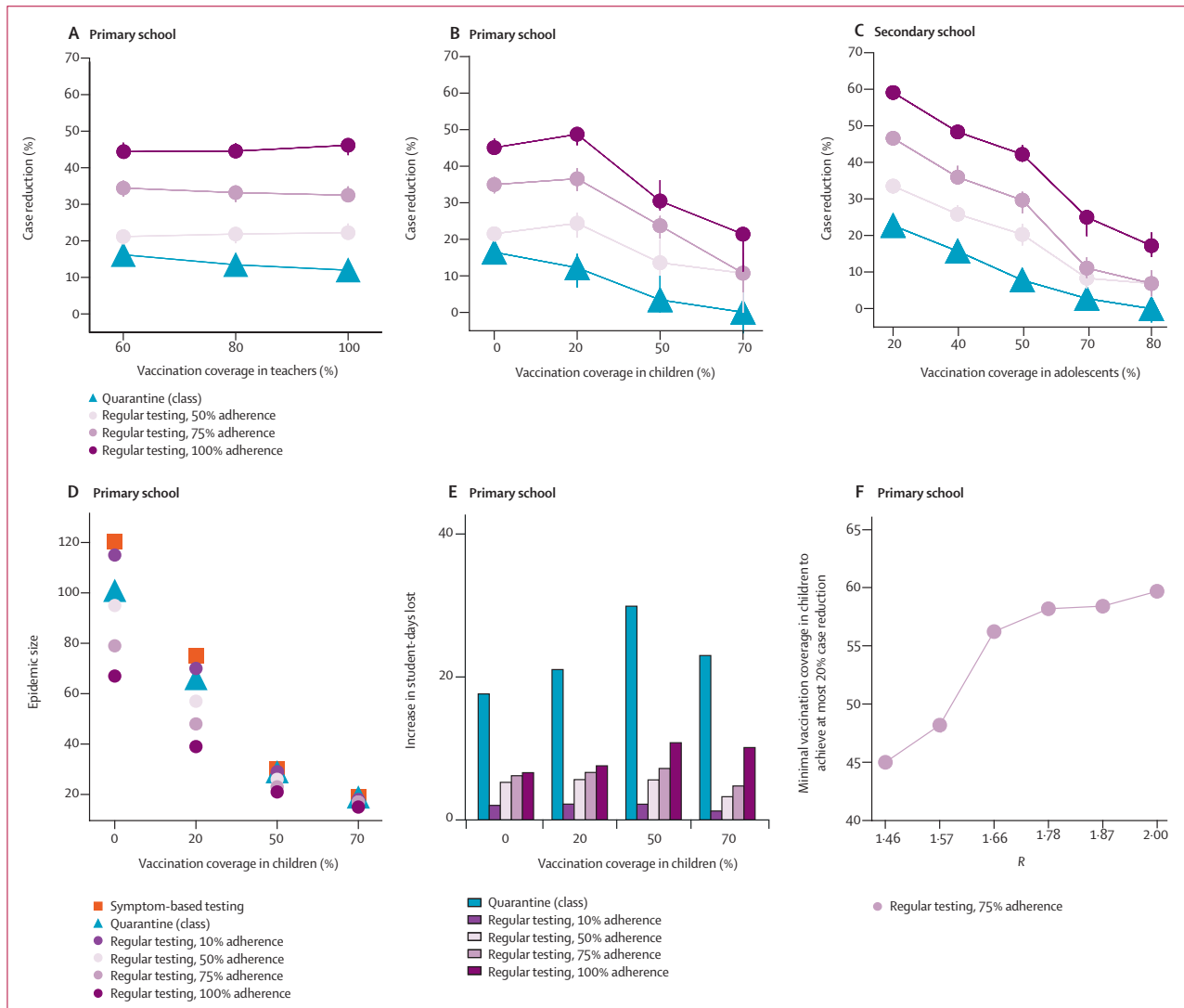


Figure 5: Impact of vaccination coverage on case reduction, epidemic size, and student-days lost

(A) Predicted case reduction relative to symptom-based testing alone for selected protocols as a function of the vaccination coverage in teachers in the primary school. (B) Predicted case reduction relative to symptom-based testing alone for selected protocols as a function of vaccination coverage in children in the primary school. (C) Predicted case reduction relative to symptom-based testing alone for selected protocols as a function of vaccination coverage in adolescents in the secondary school. (D) Predicted final epidemic size over 90 days versus vaccination coverage in children in the primary school for selected protocols. (E) Predicted increase in student-days lost relative to symptom-based testing alone for selected protocols as a function of the vaccination coverage in children in the primary school. (F) Minimal vaccination coverage in children above which regular testing with 75% adherence among the non-vaccinated in the primary school has at most a benefit of 20% case reduction, as a function of R . In all panels, simulations are parameterised with sustained introductions, all protocols include symptom-based testing, and regular testing is performed weekly. R =effective reproductive number.

and consequently in protocols' efficiencies, but protocols' ranking according to their benefit remains robust (appendix pp 48–50). High-incidence conditions due to immune evasion and higher transmissibility, compatible with an omicron scenario, confirm the value of screening with high frequency (appendix p 37).

Benefits and costs of regular testing remain stable when vaccination coverage of teachers increases from 60%

to 100% (figure 5A; appendix pp 41). Increasing vaccination coverage in students, both in primary and secondary schools, is a strong protective factor against school outbreaks (figure 5B–D), and compared with no vaccination, is expected to reduce the epidemic size by 38% (95% CI 36–40) with 20% coverage and by 75% (74–76) with 50% coverage in children under the basic protocol, considering vaccine effectiveness before waning occurs

with time (figure 5D, appendix p 40). Regular testing would provide an important supplementary control, especially while rolling out vaccination campaigns in primary schools: weekly screening 75% of non-vaccinated students would additionally reduce cases compared with the basic protocol by 36% (95% CI 32–39) with 20% vaccination coverage in children, and by 23% (20–26) with 50% coverage, without impacting student-days lost (figure 5E). Similar results are obtained with lower vaccine effectiveness (appendix p 54). The minimum vaccination coverage to reduce the benefit of regular testing to 20% case reduction or below increases with R ; for R between 1.6 and 2.0, the required coverage stabilises at around 55–60% (figure 5F).

Discussion

Strategies to safely keep schools open during the COVID-19 pandemic are a matter of controversial debate, and knowledge from the field is scarce. Using screening data from schools during the 2021 spring wave in France and empirical contact data, our study provides the first estimate of SARS-CoV-2 transmissibility in different school settings, suggesting that contacts at school increase SARS-CoV-2 transmission potential compared with transmission in the community. With countries in Europe experiencing record-high cases due to the omicron variant,¹⁴ protocols at school remain a central issue as high community transmission leaves schools vulnerable and vaccination of children progresses slowly in most countries.¹³ Our analysis indicates that regularly screening the school population is efficient in preventing infections while reducing absence from school, especially in settings where the school population is not yet vaccinated, coverage is low to moderate, or vaccine protection has largely waned.

We estimated a higher transmissibility in the school than in the community during the 2021 spring wave of the alpha variant in France. This finding suggests that repeated contacts in dense classrooms, even with facemask mandates in place, except for during sport and at lunch, favour transmission in the absence of screening protocols, with potentially high overdispersion.^{26,27} These findings align with available evidence of increased transmission in the population if schools are open.^{2,5} In the absence of vaccination, secondary school students are predicted to infect on average a larger number of individuals than primary school students, consistent with previous observations,⁷ due to age-specific epidemiological properties and contact patterns. However, more contagious variants and limited vaccination coverage in children currently put them at higher risk compared with the rest of the population, which is partially protected by vaccination. A disproportionately higher omicron circulation has been observed in children than in the general population (5500 cases per 100 000 children aged 6–10 years vs 3000 per 100 000 population in all age classes in France by mid-January, 2022) that is further sustained

by transmission at school, resulting in large school disruption,^{28,29} a higher risk of infection for students' household members,³⁰ and rapid transmission in the community.³¹ Even when conditions due to the circulating variant and vaccination coverage bring the school-specific R to below 1 (eg, as estimated under a delta wave in secondary schools in France with 77% vaccinated adolescents and high vaccine effectiveness; appendix pp 35–36), the predicted highly overdispersed offspring distribution suggests that, together with highly likely extinctions, chains of transmissions in schools are relatively rare but possible.

Using the estimated school-specific transmission rate for delta and a range of realistic epidemic conditions (with regard to introductions, seasonality, and vaccination coverage), we found that regular testing with large enough adherence provides an optimal balance in controlling school outbreaks while maintaining schools open. This finding is consistent with results showing that twice-weekly testing in England helped to control within-school transmission in secondary schools.¹² Adherence is, however, critical, suggesting that at least three-quarters of non-vaccinated individuals should participate in weekly testing to achieve a considerable case reduction. This level of adherence was not achieved in the pilot screenings in early 2021 in France. Implementing regular testing should consider improving strategies for the communication and engagement of the school community to considerably boost participation and maintain it over time.

Our findings corroborate previous numerical evidence on the value of regular testing in preventing infections.^{9–11} Our study adds to previous work by estimating the school-specific R in primary and secondary schools and integrating empirical face-to-face proximity data, allowing us to quantify individual-level variation in SARS-CoV-2 transmission. It also provides a cost–benefit analysis considering successive variants, comparing multiple protocols, and evaluating the key role of adherence in the context of partly vaccinated school populations.

Reactive class closure is highly costly in terms of student-days lost, even though detecting a case is rarer in children than in adults. Countries adopting this strategy during the omicron wave registered record-high absenteeism from school (20% of students were in remote learning in Italy in January, 2022²⁸). It also has a limited value in epidemic control, as other classes might be already affected due to unobserved introductions from the community or silent spreading within the school. The effect of silent spreading becomes particularly important when between-classes mixing is higher, as observed in the primary school. Cohorting that reduces contacts between classes is therefore an important component of school protocols, in support to screening. While regular testing detects more cases than symptom-based detection, it keeps days lost low for two main reasons. First, isolation is only applied to cases during

their infectious period, being therefore more targeted than class quarantine. Second, detecting cases that otherwise go unnoticed helps control the epidemic, breaking the chains of transmission and preventing further diffusion. As a consequence, the overall time spent in isolation is also reduced. Reactive screening, instead, would leave many cases undetected even when retesting a few days after. The iterative nature of regular testing is key to ensure control over time.

Our analysis on the omicron wave (appendix p 37) confirms the large benefit of regularly screening students compared with reactive strategies, even when these strategies are strengthened, for example, by increasing the number of reactive screenings following the index case. The reinforced reactive protocol adopted in France at the reopening of schools in January, 2022, required three screenings to be performed at days 0, 2, and 4 from detection. But under the high omicron incidence experienced at the start of 2022, this protocol led to an unprecedented demand in tests, impacting logistics, available resources, and surveillance capacity.²⁹ Our findings support instead strengthening regular screening by increasing adherence and adjusting frequency to local incidence and policy expectations, next to cohorting, facemask use, and ventilation.

Increasing vaccination in teachers protects them from infection and symptomatic disease²¹ but yields limited protection for the school population, even under full coverage. This results from the small number of teachers and the observed lower rate of interaction they have with students, and it is confirmed even when community incidence in adults is much higher than in the student-age classes. Extending vaccination to students is needed to achieve a collective benefit, reducing the likelihood and size of school outbreaks with active vaccination protection. In these conditions, regular testing would bring a supplementary control whose application should be evaluated in light of resources, logistics, adherence, epidemic conditions, and waning of vaccine effectiveness. Regular testing remains, however, critical in moderate (or lower) coverage situations, or when protection against infection has waned, as it would prevent a substantial proportion of undetected infections, having a direct impact on the school environment, reducing the number of infections and long-COVID in children,³² and an indirect impact on the community, protecting students' contacts.³⁰

This study has limitations. First, it focuses on two school settings for which empirical contact data were available, but contacts in other schools might be different, depending on the structure of curricula and the organisation of activities. Findings on the efficiency of regular testing and vaccination are, however, robust across a range of epidemic conditions and synthetic contact patterns and can thus inform on the choice of strategies to safely keep schools open. Second, data availability for the inference was limited by the pilot screening. Further work

could also focus on the downward phase of the alpha wave. Third, the study focuses on school outbreaks and it does not assess the impact that these strategies will have on the viral circulation in the community. Fourth, we did not model waning of vaccine effectiveness throughout the epidemic wave but tested lower effectiveness values that confirmed the efficiency of regular testing.

The COVID-19 pandemic will probably continue to pose a risk to the safe and normal functioning of schools. Regular testing remains a key strategy to epidemic control in school settings with moderate vaccination coverage or following waned vaccine protection, all the while minimising days lost.

Contributors

VC and AB conceived and designed the study. EC, GB, and VC accessed and verified all the data and were responsible for the decision to submit for publication. EC, GB, DAC, and CP analysed the data. EC, GB, P-YB, and VC developed the inference framework. EC and DAC developed the code. EC and GB performed the numerical simulations and analysed the results. All authors interpreted the results. VC wrote the Article. All authors contributed to and approved the final version of the Article.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified individual data on contacts of the two schools under study are publicly available at the SocioPatterns project website (<http://www.sociopatterns.org/datasets/>). De-identified aggregated COVID-19 community surveillance data by age class are publicly available at Santé publique France data observatory platform (<https://geodes.santepubliquefrance.fr/>). De-identified aggregated COVID-19 prevalence data from pilot screenings during the alpha wave used in this study are available in the tables reported in the appendix (pp 24–25).

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3.3 Discussion

This study aimed to provide an estimation of the transmissibility of COVID-19 within primary and secondary schools during the outbreak of the Alpha variant in France. To achieve this, we used prevalence data collected from schools during the same period. Additionally, we incorporated information from the existing literature on the transmission advantage of the Delta variant to reproduce how this variant spread more easily. By employing these data and considering the potential impact of more infectious variants, we evaluated and compared the effectiveness of various school strategies in terms of transmission and educational outcomes. Our analysis allowed us to anticipate the response of these strategies for the academic year 2021-2022. In particular, implementing weekly screening proved to be the most effective option for minimizing disruptions to education and reducing the number of infections in schools.

The estimation of the effective reproductive number in schools, denoted as R_{school} , provided an assessment of transmission levels in primary and secondary schools with the use of face masks and reactive class closure measures in place. The findings showed that both types of schools had transmission levels above the epidemic threshold of 1 during the Alpha variant outbreak, highlighting the potential contribution of school contacts to COVID-19 transmission. These results were in contrast with some studies on the first wave and the first trimester after the school reopening in September 2020. With respect to the first wave, in a study conducted in New South Wales, Australia [161], the child-to-child transmission rate was estimated to be 0.3% among the pediatric population attending schools or early childhood education and care facilities while infectious. However, during the first wave, distance learning was implemented in March 2020, and in-person attendance was reduced, which could have affected the estimation of intra-school transmission. Moreover, testing of case contacts was conducted only after symptom manifestation. Similarly, the study in Catalonia carried out after the school reopening found low transmission levels within class bubbles, with R ranging from 0.2 in preschool to 0.6 in high school [162]. As in the previous study, some limitations could have affected the results. In particular, the symptomatic-oriented testing strategy may have missed other forms of infections. Moreover, the screening of bubble contacts had occurred only after the identification of symptomatic cases.

In our study, we moved away from the initial narrative that downplayed the role of schools and children in COVID-19 transmission. We demonstrated the potential for transmission events within schools when adequate control measures were not in place. Subsequent studies reached similar conclusions regarding school transmission. For instance, outbreaks in primary schools in the Netherlands during the Alpha variant showed high attack rates (ARs) within classes [163]. These outbreaks were likely facilitated by factors such as the lack of mandatory masking for children, insufficient ventilation, and the mixing of children during breaks and sports activities. Additionally, high secondary attack rates (SARs) were observed in household contacts of staff members and children, indicating that school-acquired infections could contribute to community transmission. Moreover, evidence from the Schools Infection Survey (SIS) from November 2020 to June 2021, further supported the

potential for school-based transmission of SARS-CoV-2, especially when community infection levels were high [164]. Conversely, a lower in-school prevalence was recorded among secondary school students in the spring and summer of 2021 when biweekly screening was implemented, compared to previous rounds during the fall term of the 2020 school year. Similarly, a modelling study calibrated on data collected in England following the reopening of schools in March 2021 after the third lockdown found evidence of reduced transmission within schools if more stringent measures were in place [165]. These measures included mask-wearing, self-isolation of close contacts, and regular screening with lateral flow tests (LFDs). These findings, along with our own, hence highlighted the need to explore alternative strategies to class closure and shift towards screening testing rather than relying on diagnostic symptomatic testing to reduce the spread of the virus in schools.

Our cost-effectiveness analysis in a Delta scenario suggested that systematic screening of unvaccinated school populations was the most effective solution for controlling school infections and absences, considering various circumstances such as community introductions and seasonal R_{school} values. Other modelling studies from different countries and from the same period as our preprint confirmed that regular screening was highly effective in reducing cases. For example, a study based on a compartmental model recommended regular screening for planning the return to university residences during the fall of 2021 in the US [166]. Additionally, two distinct agent-based models comparing different test interventions in primary and high schools in the US found regular screening to be an effective measure for reducing transmission on school campuses and within households [167, 168]. However, it should be noted that these agent-based models did not incorporate empirically measured school interactions and relied on assumed levels of epidemic activity instead of calibrating the model on prevalence data. Nevertheless, these studies concluded that weekly screening could facilitate in-person education with controlled transmission risk. This result was confirmed by a subsequent modelling study in a simulated primary school, showing that systematic screening could reduce the infection attack rates [169].

We showed that incidence conditions could influence the benefits of screening. In low transmission conditions with few circulating cases or high transmission conditions with a large number of cases, the attractiveness and control power of screening may diminish. This was also supported in a subsequent cost-effectiveness analysis for K-12 Schools in California [170]. We will explore the responsiveness of weekly screening under high-incidence conditions in Chapter 4 and Chapter 5.

Additionally, we emphasized that the engagement and uptake of screening initiatives were critical factors for ensuring their effectiveness. By integrating empirical adherence data from a pilot screening campaign in France during the Spring of 2021, our model showed that the participation levels in secondary schools were insufficient to guarantee the success of weekly screening. To compensate for low adherence, we proposed increasing the frequency of screenings to achieve a similar level of control. This finding provided useful insights for policymakers who planned to implement school screening the following year to address negative attitudes towards it. In the modelling study analyzing swab data and

absences from biweekly screening in England during the Alpha wave, adherence in secondary schools was estimated nationally at 36% [165]. Conversely, adherence seemed to be higher in primary schools participating in the pilot campaign in France (approximately 50% on average) and even higher during the experimental weekly screening in fall 2021 during the Delta and Omicron waves [72] (see Chapter 5). Also the observed adherence in primary school children during a weekly screening regimen in the Basel canton, Switzerland, was high (on average 75% in 2021, see Chapter 4). Finally, a survey launched in September 2021 in Germany, aimed to assess the acceptability and feasibility of saliva pool testing in primary schools, found that 80% of participants, including parents, teachers, and school principals, supported the use of regular saliva-based screenings [171]. Despite the favorable response, it is important to acknowledge that adherence to testing protocols may be lacking in real-world scenarios. Outside Europe, for instance, a school-based testing program conducted across six pilot sites in the US between October 2020 and June 2021 reported participation rates ranging from less than 1% in New Orleans to about 68% in Los Angeles among students [172].

The choice of test type could also have played a role in promoting higher adherence rates in French primary schools. The debate surrounding the preferred test type was a topic of extensive discussion during the pandemic. A thematic analysis of social media data and online newspaper comments examining public perceptions of asymptomatic testing in schools in England identified anxiety over testing among the initial negative barriers that could have hindered adherence [173]. Saliva PCR tests were employed in primary schools in the Basel canton in Switzerland and in Germany due to their perceived child-friendly nature and ease of administration compared to rapid antigen tests with nasal swabs [171, 174]. Saliva tests were later applied by authorities when weekly screening was trialed in the experimental schools in France during the fall of 2021 (see Sections 1.3.2 and 2.1.1). Conversely, in secondary schools, we considered rapid lateral flow devices (LFDs) which were used in England, Austria, and France despite their lower test sensitivity compared to the gold standard of PCR testing. Although the use of LFDs was met with some criticism due to their reduced sensitivity, it was demonstrated that this drawback was offset by their rapid turnaround time, which allowed for the prompt identification and isolation of infectious individuals while curbing the spread of infections [175]. Furthermore, LFDs were shown to be better suited for screening purposes, as they were more likely to detect individuals during their infectious period. In contrast, PCR tests might capture residual viral loads, returning positive results even when individuals were no longer infectious [176].

Finally, our cost-effectiveness analysis classified reactive class closures as the most expensive measure in terms of lost days without providing any substantial advantage in epidemic control, and forcing the isolation of unaffected students. Reactive screening could reduce the loss of days but did not lead to any significant gain in control because it was not sufficiently targeted for the identification of asymptomatic cases.

In the revision of the manuscript, we repeated the analysis by adding the impact of vaccination on children and adolescents. This analysis was particularly valuable in November

2021 as it provided evidence-based recommendations to support the authorization for expanding vaccination to children in France [14]. Based on predominantly US sources where children vaccination approval was granted early [177], we demonstrated the potential benefits of vaccinating this age group if the vaccine protection in children was equivalent to that in adults. We also identified the required vaccination coverage to eliminate screening, which was approximately 55%. However, this threshold was never reached in children in Europe. By April 2022, the median vaccination coverage had stagnated at approximately 13% in the 27 reporting European countries [178], and no significant increase was observed until May 2023, when the World Health Organization (WHO) officially declared the end of the COVID-19 emergency [179]. With the emergence of the Omicron variant and the accumulation of new evidence, the effectiveness of vaccines in children appeared to be lower and diminish rapidly over time [93, 94]. The waning of vaccine effectiveness over time will be considered and included in the model in Chapter 5. Regarding adolescents, by the start of the 2021 academic year, 50% of adolescents in France had completed the primary vaccination course. This percentage rose to 75% in December 2021, coinciding with the emergence of the Omicron variant [99]. Based on the vaccination coverage and the findings from our analysis, it is plausible that teenagers were better protected during the Delta wave in the fall, in comparison to children. This observation gained support from the examination of the incidence rate among this age group in other European countries where vaccination rates among adolescents were notably high. For instance, Denmark, which exhibited higher vaccination coverage among adolescents than Norway, experienced low incidence rates in the 12–15 and 16–17-year age brackets, despite both countries having implemented routine screening for school-aged children [149]. Finally, our analysis revealed that the vaccination of teachers did not have a substantial impact on the size of the epidemic, although it did contribute to the reduction of transmission among teachers. Similar findings were reported in a concurrent study conducted in the United States in a Delta scenario [180]. These results therefore highlighted the possible ineffectiveness of prioritizing teacher vaccinations as a means of safeguarding children from infection.

We acknowledged that this study had some limitations, as outlined in Chapter 2 and Section 3.2. In a related work, we demonstrated that implementing cohorting, which involved limiting mixing across classes and reducing contact duration, could further enhance the effectiveness of control strategies [15]. Additionally, school size or structure may vary in different countries. Although we did not assess the effect of school size in this study, similar conclusions regarding the effectiveness of screening were drawn from a larger simulated US primary school with approximately 600 students, 60 teachers/staff, and 30 classes [180]. While we did not explicitly model airborne transmission, considering that school networks were nearly fully connected, this route was likely absorbed by contacts. However, we were unable to explicitly assess the role of mask-wearing and ventilation systems, which was recommended in schools in France [181]. Furthermore, we assumed that children were less susceptible and had lower infectiousness [81, 82, 108, 109, 110, 115]. To cover the uncertainty about the relative susceptibility and infectiousness of children and adolescents, a wide sensitivity analysis was performed. Even when we considered larger susceptibility

and infectiousness in children and adolescents, regular screening was confirmed to outperform the other protocols. Finally, other sources of costs were not considered, such as test costs or resources. We will consider this aspect in the following Chapter.

In conclusion, this study provided guidelines on how to contrast school infections in light of the need of minimizing school disruption and its side effects using both non-pharmaceutical and pharmaceutical interventions. In particular, the study showed that transmission in schools could occur and the activation of reactive strategies in response to a symptomatic case was not sufficient to contain it. Alternatively, it highlighted the importance of reevaluating the role of children as a target population for extensive school screening to protect children from infections, allow in-presence learning, and mitigate the risk of wider outbreaks in the community. These elements were especially valuable as, at that time, schools and communities were still struggling with the emergence of new COVID-19 variants and a delayed vaccine rollout for young children.

Optimizing test resources and control under high incidence conditions due to Omicron wave

In this chapter, I present an extended version of the transmission model that was calibrated to replicate the high incidence rates in children experienced during the Omicron wave in France in early 2022. To ensure a comprehensive analysis of the European incidence conditions, the study was expanded to include smaller and higher incidence levels. Unlike the previous work, which analyzed the trade-off between infections and absences in a Delta scenario, here we compare three school protocols adopted by Italy, Basel Canton, and France during the Omicron wave. The objective was to test how they responded during the peak phase in terms of the resources required to implement each school strategy while controlling cases and minimizing school days missed. This work was published as a research article in the *Eurosurveillance* journal [7].

4.1 Introduction

In early January 2022, the BA.1 Omicron variant caused an unprecedented rise in COVID-19 cases among children in several European countries, leading to a significant disruption to normal school activities. This was exacerbated by the fact that children had the lowest rates of vaccination coverage in Europe, as their approval and rollout of vaccines occurred later compared to other age groups [178]. While the canton of Basel in Switzerland had already switched to salivary testing strategies every week since May 2021 [182], other countries such as Italy maintained a more conservative approach to address the rising case burdens, consisting of the application of reactive class closure despite the large disruption that could derive [183]. France instead decided to strengthen the reactive screening strategies proposed at the end of 2021, increasing the number of control tests after the identification of a symptomatic student in a class. In turn, this approach led to a rapid surge in test demand and widespread class or school closures due to the exceptionally high number of cases.

These different approaches taken by various countries provided valuable examples of diverse strategies implemented in schools, each potentially producing distinct outcomes. Consequently, there was a need to reassess school strategies and provide guidance to decision-makers to identify the optimal solution, considering the intense levels of epidemic activity and the defined objectives.

The objective of this study was to address the question of resources needed to sustain testing programs in order to maximize in-person educational time while effectively controlling COVID-19 transmission and minimizing operational challenges during periods of high incidence. The three aforementioned school protocols (weekly screening, reactive class closure, and reactive screening strategies) were examined as case studies. The agent-based model presented in Chapter 3 was adapted to simulate the circulation of the Omicron variant in schools (including reinfection, shorter generation time, etc.), and the protocols were compared in terms of their ability to prevent cases, minimize the number of student days lost, and determine the testing volume in the peak week. The impact of vaccination was also taken into account in the analysis.

4.2 Article #2: Minimising school disruption under high incidence conditions due to the Omicron variant in France, Switzerland, Italy, in January 2022

Minimising school disruption under high incidence conditions due to the Omicron variant in France, Switzerland, Italy, in January 2022

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Background: As record cases of Omicron variant were registered in Europe in early 2022, schools remained a vulnerable setting undergoing large disruption. **Aim:** Through mathematical modelling, we compared school protocols of reactive screening, regular screening, and reactive class closure implemented in France, in Baselland (Switzerland), and in Italy, respectively, and assessed them in terms of case prevention, testing resource demand, and schooldays lost. **Methods:** We used a stochastic agent-based model of SARS-CoV-2 transmission in schools accounting for within- and across-class contacts from empirical contact data. We parameterised it to the Omicron BA.1 variant to reproduce the French Omicron wave in January 2022. We simulated the three protocols to assess their costs and effectiveness for varying peak incidence rates in the range experienced by European countries. **Results:** We estimated that at the high incidence rates registered in France during the Omicron BA.1 wave in January 2022, the reactive screening protocol applied in France required higher test resources compared with the weekly screening applied in Baselland (0.50 vs 0.45 tests per student-week), but achieved considerably lower control (8% vs 21% reduction of peak incidence). The reactive class closure implemented in Italy was predicted to be very costly, leading to >20% student-days lost. **Conclusions:** At high incidence conditions, reactive screening protocols generate a large and unplanned demand in testing resources, for marginal control of school transmissions. Comparable or lower

resources could be more efficiently used through weekly screening. Our findings can help define incidence levels triggering school protocols and optimise their cost-effectiveness.

Introduction

At the start of 2022, countries in Europe faced large disruptions in schools due to the exceptionally high incidence rates of the severe acute respiratory coronavirus 2 (SARS-CoV-2) Omicron variant (Phylogenetic Assignment of Named Global Outbreak (Pango) lineage designation: B.1.1.529) [1]. As the adult population was largely covered by vaccination, higher incidence rates were reported for the first time in children and adolescents compared with other age groups [2]. In France, nearly 7,000 coronavirus disease (COVID-19) cases per 100,000 were reported among 6–10-year-old and 11–19-year-old individuals at the peak of the Omicron wave in January 2022, compared with ca 4,500 cases per 100,000 among the 20–59-year-olds [3]. Despite protocols implemented by national authorities to ensure in-person attendance in schools, school establishments were nevertheless put under pressure by the high incidence rates. Protocols required repeated quarantines, disrupting attendance and learning, or led to large and sudden testing demands for children, overloading saturated surveillance systems [4,5].

Through modelling, here we compared the school protocols adopted by France, Switzerland, and Italy, in

terms of resource peak demands, infection prevention, and reduction of schooldays lost, under the high incidence conditions experienced in January 2022 during the Omicron BA.1 variant wave.

Methods

Modelling SARS-CoV-2 transmission in schools

We adapted to the Omicron wave a stochastic agent-based model of SARS-CoV-2 transmission at school presented in detail by Colosi et al. [6]. The model uses empirical data on time-resolved face-to-face proximity contacts between individuals in a primary school in France, collected using wearable radio frequency identification (RFID) sensors [7]. The dataset includes 232 students (aged 6–10 years) and 10 teachers organised in 10 classes, two classes per grade. Students were found to spend on average more time interacting with other students of the same class than across classes, and to establish longer contacts compared with teachers [6]. We described SARS-CoV-2 infection progression through the following disease stages: latency, prodromic stage, clinical and subclinical stages, recovery from infection (Supplement 1.1. Compartmental model and parameters). Stages were informed from empirical distributions, and accounted for age-specific estimates of susceptibility, transmissibility, probability of developing symptoms, and probability to detect a case based on symptoms [8–18].

We modelled the circulation of the Omicron variant, considering 20% protection after infection from prior variants [19], an intrinsic transmissibility advantage of 30% relative to the Delta variant (Pango: B.1.617.2) [20], and a shorter incubation period of 0.5 days compared to the Delta variant [20,21]. Omicron's higher spreading rate was considered to be mainly due to immune evasion [20], in line with observations from household studies [22], but we also tested a transmissibility advantage of 80% relative to Delta for sensitivity (Supplemental Table S1. Parameters, values and sources used to define the compartmental model). The transmissibility advantage was applied to the within-school transmissibility of previously circulating variants that we inferred in prior work from observed prevalence in French schools [6]. We calibrated the model to reproduce the reported community surveillance incidence in primary school students (6–10 years old) in France in January 2022 [3], and considered additional scenarios of Omicron waves reaching lower and higher peaks to capture the variability of the wave across European countries [2]. Additional details are provided in the online Supplement (section 3.1. Incidence and number of tests per student over time under different introduction conditions).

School protocols

We modelled the school protocols adopted in France, in the Baselland canton in Switzerland, and in Italy. We simulated the reactive protocol applied in France in January 2022, requesting an anterior nasal lateral flow

device (LFD) test at days D_0 , D_2 , and D_4 to the class of the detected case, following case identification [23]. Students with positive tests had to isolate for 7 days. For sensitivity, we tested reactive screening with different numbers and lags for control (D_0 , D_3 , D_7 and D_0 , D_4 , see Supplement 4.5. Sensitivity analysis on control screening). In Baselland, students were tested on a voluntary basis every week with salivary PCR tests [24]. We thus simulated a regular screening strategy, considering two options for the frequency of screening, once a week (as in Baselland), and twice a week, with a 75% adherence of the school population (min–max range of 50–100%). Regular screening was performed on all participating individuals, regardless of the presence of symptoms. Students with positive tests were isolated for 7 days. Finally, we simulated the reactive class closure adopted in Italy, requiring a quarantine of 10 days for the students of the class of the detected case [25]. These protocols were considered independently in the analysis, as each corresponded to a national strategy. In all cases, we also considered symptomatic testing and case isolation.

The model was informed with time-varying and age-dependent test sensitivity, yielding an estimated 67% peak sensitivity for asymptomatic children in nasal LFD tests and 96% in salivary PCR tests [26] (Supplement 1.5. Parameters for screening and testing protocols). We also explored a lower peak sensitivity of 55% for LFD tests.

Vaccination

The model was further stratified to account for vaccination status and to include vaccine effectiveness (VE) against infection and transmission (Supplement 1.6. Vaccination). By the first week of January 2022, 94% of adults (18–59 years) in France were vaccinated with at least two doses, and 45% had received the third dose since the opening of the vaccination campaign on 27 November 2021 [27]. We therefore considered in the model that all teachers completed the primary vaccination, with 50% of them having received also the third dose, i.e. the booster. As adults were recently boosted, we considered the following values for the VE against infection: a VE of 70% for teachers vaccinated with three doses, corresponding to the estimate within the first 4 weeks since the third dose [28]; a VE of 15% for those with two doses only, corresponding to the estimated waned efficacy at 6 months after the second dose [28]. For sensitivity, we varied the booster vaccination coverage in teachers up to 100% (Supplement 4.1. Sensitivity analysis on vaccination coverage for teachers).

The vaccination campaign in children (5–11 years) opened on 22 December 2021 [29]. By mid-January 2022, the coverage in this age group in France was <3% [3], therefore we assumed no vaccinated children in the main analysis. We then tested higher vaccination coverages (20%, 40%, 60%) in children in the scenario analyses, considering high (VE=50%, estimated

KEY PUBLIC HEALTH MESSAGE

What did you want to address in this study?

During January 2022, the high incidence of SARS-CoV-2 Omicron variant infections led to school disruptions in many European countries. Authorities thus implemented protocols to lessen the virus spread in school settings. We wished to understand which of three widely used protocols, performed best, considering test demand, infection prevention, and school absences. The protocols included 'reactive screening', 'weekly screening' and 'reactive class closure'.

What have we learnt from this study?

When incidence of SARS-CoV-2 infections is high, school protocols based on reactive screening lead to a substantial and unplanned demand for testing resources, while little infection prevention is achieved. With the same resources, proactive weekly screening considerably reduces the peak of infections, limiting schooldays lost. Reactive class closure leads to large disruption with successive closures.

What are the implications of your findings for public health?

Our findings provide key information to improve prevention and control strategies of SARS-CoV-2 transmission in the school setting. They can be used to tune the response by defining incidence levels triggering school protocols, depending on the severity of the circulating variant and according to the objectives established by authorities.

within the first 4 weeks from vaccination [30]) and low (VE=20%) values of VE against infection.

Results

Simulations capture well the reported dynamics of community surveillance incidence in primary school students (6–10 years) in France (Figure 1A). The reactive protocol implemented by authorities was predicted to marginally reduce the peak, whereas regular screening would flatten more substantially the curve. The median number of tests required by the reactive protocol increased along the wave, with a predicted peak demand of 0.50 (interquartile range (IQR): 0.32 to 0.71) tests per student per week at the incidence rate experienced in France (ca 7,000 cases per 100,000 among 6–10-year-olds; Figure 1C). Test demand instead was predicted to decrease in the regular protocols because fewer students would be present in class after the peak of infections due to isolation, with 0.45 (IQR: 0.42 to 0.47) tests in the once-a-week screening and 0.96 (IQR: 0.91 to 1.02) in the twice-a-week screening. We found that higher incidence conditions could lead to a larger demand of tests by the reactive protocol compared with the weekly screening (Figure 1B,D).

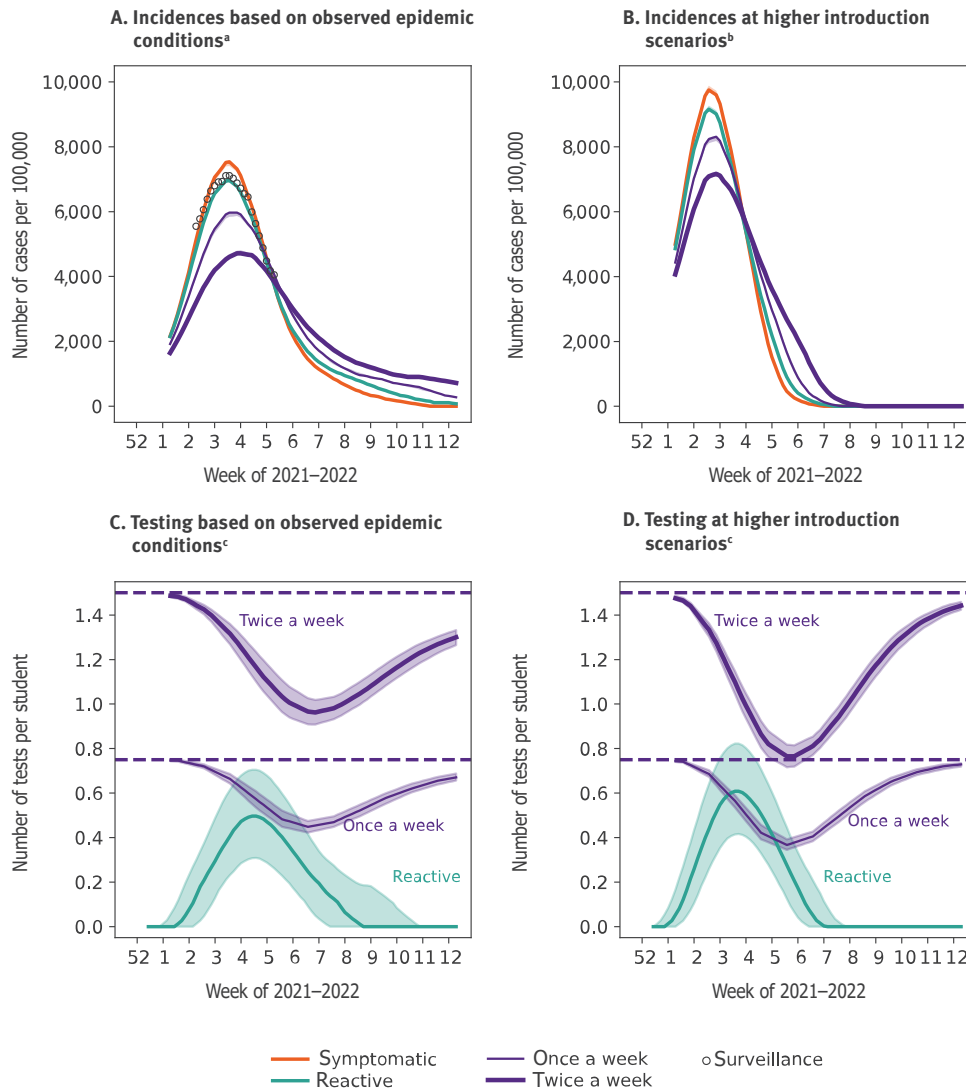
To evaluate how to best use resources, we estimated the impact of protocols in reducing the peak incidence and extended the analysis of Figure 1 to a larger set of Omicron wave scenarios with varying peak incidence. For the incidence rates registered in France in January 2022, reactive screening was estimated to lower the

peak by 8% (IQR: –3% to 19%), compared with 21% (IQR: 11% to 31%) reduction achieved by the weekly screening (Figure 2A,B), despite the higher demand in testing resources at the peak (0.50 vs 0.45 tests per student-week, respectively).

The predicted number of tests required by the reactive screening would increase for increasing values of the incidence rate (from 0.31 to 0.65 tests per student-week corresponding to 5,000 to 10,700 cases per 100,000), but they would achieve a marginal control of the viral circulation at school, reducing the peak of the wave by at most 12%. Results would not change by changing the lags of the reactive screening (Do, D3, D7 vs Do, D2, D4) but peak reduction would be even lower if a lower number of screenings was adopted (Do, D4; Supplement 4.5. Sensitivity analysis on control screening). Regular screening would instead achieve 20% or more of peak reduction for incidence rates up to 7,500 cases per 100,000 with a weekly frequency, and for rates up to 10,100 cases per 100,000 if screening the school twice a week. Similar results were obtained considering the reduction of the epidemic size of the full wave and a higher transmissibility advantage of the Omicron variant (Supplement 3.2. Test needs and schooldays lost vs. percentage of case reduction at varying incidence rate and, Supplement 4.2. Sensitivity analysis on advantage in transmission rate of Omicron relative to Delta).

FIGURE 1

Incidence of COVID-19 cases among 6-10-year-olds and number of tests per student over time under different school protocols, France, January 2022



COVID-19: coronavirus disease; IQR: interquartile range; LFD: lateral flow device.

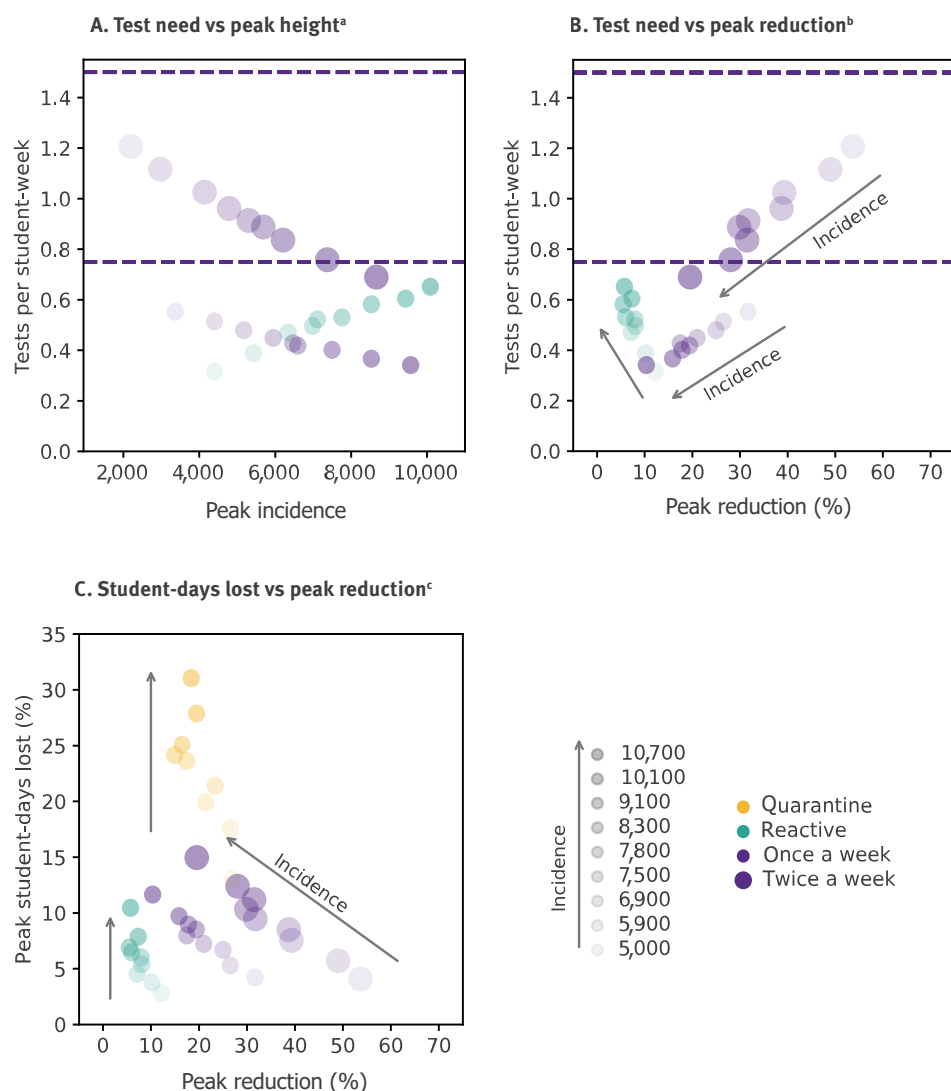
^a Simulated weekly incidence expressed in number of COVID-19 cases in students per 100,000 over time for different protocols, and reported incidence in the 6–10-year age group in France in the period 10 Jan–6 Feb 2022 [3]. The reactive protocol, applied in France, is calibrated to surveillance data.

^b As in A for simulated scenarios at higher introduction conditions.

^c Panels C,D: average number of tests per student over time for reactive and regular protocols under the epidemic conditions illustrated in panels A and B respectively. The horizontal dashed lines indicate the theoretical values of the demands in number of tests per student, in the screening once a week and twice a week (i.e. imposed by 75% adherence and by the frequency). Results are obtained considering the use of nasal LFD tests in both reactive and regular screenings. Shaded areas around the curves correspond to the IQR.

FIGURE 2

Test needs and schooldays lost vs peak reduction at varying peak incidence rates



COVID-19: coronavirus disease.

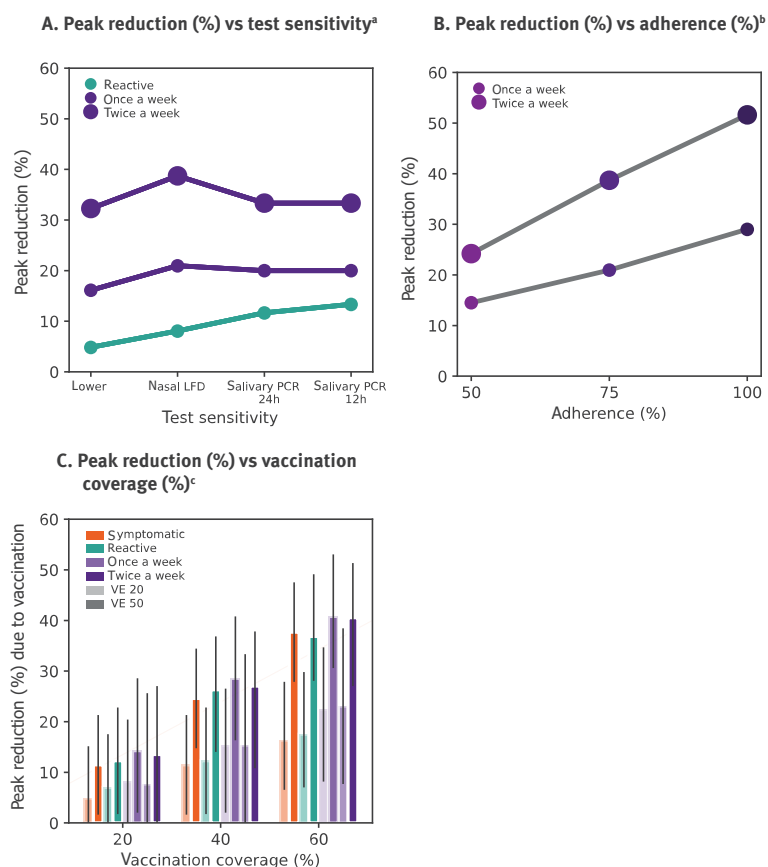
^a Demand in the number of tests per student-week at peak as a function of the peak incidence (COVID-19 cases in students per 100,000) for the reactive protocol and the regular screening protocols with once a week and twice a week frequency. The horizontal dashed lines indicate the theoretical values of the number of tests per student in the regular screening (i.e. imposed by 75% adherence and the frequency). Dots reduce their transparency for increasing incidence.

^b Demand in the number of tests per student-week at peak as a function of the percentage of peak reduction achieved by each protocol compared with symptomatic testing (i.e. in absence of interventions), for different incidence levels. The horizontal dashed lines are as in panel A. Dots transparency code is the same as in panel A.

^c Peak percentage of student-days lost as a function of the percentage of peak reduction achieved by each protocol compared with symptomatic testing, for different incidence levels. The reactive quarantine of the class is shown as an additional protocol. Arrows are shown as a visual guide.

FIGURE 3

Impact of test sensitivity, adherence to regular screening, and vaccination



LFD: lateral flow device; Pango: Phylogenetic Assignment of Named Global Outbreak lineage designation; VE: vaccine effectiveness.

^a Percentage of peak reduction achieved by each protocol compared with symptomatic testing (i.e. in absence of interventions) as a function of the test sensitivity and of the delay in returning the results (12 h from testing, 24 h from testing for PCR tests). The lower value corresponds to 55% peak sensitivity.

^b Percentage of peak reduction as a function of adherence to regular screening.

^c Percentage reduction in the peak incidence for each protocol due to vaccination in children, for different vaccination coverages at respective values of VE of 50% (solid bars) and 20% (transparent bars).

Results of all panels refer to the Omicron (Pango lineage designation: B.1.1.529) wave shown in Figure 1A.

Student-days lost remained below 12% with reactive and weekly screening, whereas reactively closing the class as in the Italian protocol could lead to >20% of absence per student if peak incidence is over 7,500 cases per 100,000 (Figure 2C). Findings were robust against changes in booster coverage in teachers, in Omicron transmissibility and incubation period (Supplement 4.1, 4.2, 4.3). Higher detection rates would penalise the reactive screening, due to an increase in test demand while control would remain limited (Supplement 4.4).

Changing from nasal LFD tests to salivary PCR tests would improve the reactive strategy from 8% to 13% peak reduction if results were available after 12 h (Figure 3A). Instead, regular testing was predicted to be mainly affected by adherence to screening (Figure 3B). Vaccinating 6–10 years old children was predicted to provide a collective benefit in reducing viral circulation at school. If children were vaccinated close to the epidemic wave (therefore with an estimated VE of 50% for children within 4 weeks after the second dose), the peak would be reduced by ca 30% for 40% coverage and by ca 40% for 60% coverage, compared with no

vaccination (Figure 3C). If vaccination occurred long before the epidemic wave (waned vaccine effectiveness $VE=20\%$), the reductions would be smaller, around 15% and 20% for 40% and 60% coverage, respectively.

Discussion

For the high incidence rates recorded in January 2022 in Europe due to the Omicron BA.1 variant, our study predicted that reactive screening strategies in schools, as employed in France, required a higher number of tests per student per week compared with weekly screening, but achieved a lower epidemic control. The protocol requesting three tests in less than a week for case contacts in French primary schools led to large disruption events in January 2022, in terms of logistics, resources, and impact on surveillance capacity [4]. We estimated that the same resources would have been more efficiently used by weekly screening schools, reaching 21% peak reduction for the incidence rates registered in France in January 2022, compared with the marginal reduction (8%) estimated for the reactive screening.

Reactive screening is predicted to be poorly effective in case prevention for two main reasons. First, timely interventions of case identification and isolation are key to control SARS-CoV-2 spread, given the presence of pre-symptomatic and subclinical transmission [31]. Reactive strategies suffer from considerable time lags compared with the ongoing transmission dynamics. Second, this aspect is particularly challenging in children as they have a lower probability of developing symptoms [12,13,15,17,32], and therefore of being identified as possible COVID-19 cases compared with adults. By the time the screening is activated, after the detection of a case based on recognisable symptoms, the transmission may have already occurred in the school and have previously generated asymptomatic infections that went unnoticed. That is, the case triggering the screening does not necessarily represent the start of the chain of transmission and may instead occur after few generations of cases that are not discovered by surveillance, or following undetected introductions. On the contrary, regularly screening the school every week or twice a week allows the prompt identification and isolation of infectious individuals regardless of their symptoms [6,32-39]. As more cases are found, onward transmissions are more efficiently prevented, with a higher efficiency if frequency of screening is higher. The capacity of screening (whether reactive or proactive) to reduce the peak incidence decreases for increasing values of the incidence rates. Higher incidence in the community indeed corresponds to larger rates of introductions in the school, which require an even more rapid response for the identification of cases to prevent onward transmission [6].

Some countries opted for systematically screening schools against SARS-CoV-2 transmission, supported by numerical evidence [6,32-39]. Authorities in Baselland (Switzerland) offered weekly salivary PCR

tests to all schools since March 2021. Prior to making participation mandatory in 2022, recorded adherence was on average rather high (>75%) [24]. Proactively screening also has the advantage of planning resources in advance, contrary to reactive screening subject to sudden peak demands and potential shortages. This was reported to help simplifying the logistics of test-to-stay strategies in pilot weekly screenings implemented in a number of pre-primary and primary schools in the Auvergne-Rhône-Alpes region in France in December 2021. Preliminary unpublished empirical estimates from these screenings also suggest a reduction of cases during the Delta wave in December 2021 compared with the reactive strategy, in line with model predictions.

The widespread access to nasal antigenic tests made repeated self-testing possible without loss in efficiency, as lower sensitivity is compensated by promptness of results and high frequency [40]. Regular self-testing would also limit the high rates of absence from school that are associated to reactive class closures. Without test confirmation, reactively closing the class imposes the quarantine to likely uninfected students who would unnecessarily miss school while transmission may have already occurred in other classes due to cross-classes contacts or through introductions [6]. Under the high incidence rates registered in the Omicron wave, our model predicted multiple class closures continuously disrupting the school rhythm and impacting students' learning, with more than 20% of schooldays lost per student, compatible with observations in Italy during that wave [5].

This study focused exclusively on the school setting, and did not assess the impact that protocols at schools, aimed at limiting school transmission, may have on the epidemic dynamics in the community. Model-based findings previously highlighted that protocols mitigating viral circulation at school also reduce the spread in the community [34,41,42]. Conversely, increased transmission in the community was found to be associated to schools in session [43,44], and households with children were estimated to be at higher risk of SARS-CoV-2 infection [45], suggesting that a considerable fraction of transmission events originated from the school setting [46]. The analysis of a school outbreak in early 2021 in a municipality in the north of Italy estimated that ca 21% of SARS-CoV-2 transmissions were associated with school contacts, compared with 50% and 29% transmissions associated with household and community contacts, respectively [47]. Combined with the above evidence, our findings therefore suggest that implementing strategies to control transmission at school will reduce the potential for seeding transmissions from schools to other settings, narrowing the spread across households [48] and the risk of reaching individuals at risk of COVID-19 complications.

Our findings can be used to tune the response by defining incidence levels triggering protocols if facing a high

incidence wave, depending on the severity of the circulating variant and according to the objectives established by authorities. Systematically screening schools remains the optimal test-to-stay strategy, reducing peak incidence rates in children, and thus their consequences on hospitalisations [49] and long COVID [50] in this age group, while limiting school disruption and requested resources. Large vaccination coverage in children contributes to mitigate high viral circulation, making schools safer. Coverage remains, however, low in children in several European countries (16% median coverage for 2-dose vaccination in 5–9 years old by the start of September 2022; Supplement S9. Vaccination coverage of children in Europe).

Our study has limitations. We did not consider immunity waning over time as we focused on a single pandemic wave, but tested low vaccine effectiveness to account for the estimated reduction associated with the lag from the last vaccination dose. Our results are framed within the context experienced by European countries. As such, results are not directly applicable to other countries with a context of lower population immunity due to the limited spread of earlier variants. In previous work, however, we showed that conclusions are qualitatively robust, with regular screening strategies outperforming reactive strategies in case prevention under a set of different epidemic and immunisation conditions [6].

A large demand in tests results from reactively screening schools in high incidence conditions. Comparable resources could be more efficiently used in a proactive screening strategy to mitigate the peak.

Ethical statement

The contact study was approved by the Commission Nationale de l'Informatique et des Libertés (the French national body responsible for ethics and privacy; 1719527 and 1427054) and school authorities. Informed consent was obtained from participants. No personal information of participants was associated with the RFID identifier.

Data availability

De-identified individual data on contacts of the primary school are publicly available at the SocioPatterns project website (<http://www.sociopatterns.org/datasets/>). De-identified aggregated COVID-19 community surveillance data by age class in France are publicly available at Santé publique France data observatory platform (<https://geodes.santepubliquefrance.fr/>).

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Conflict of interest

None declared.

Authors' contributions

V.C. conceived and designed the study. E.C., G.B. analysed the data. E.C. developed the code. E.C., G.B. performed the numerical simulations, and analysed the results. E.C., G.B., A.B., B.L., P.V., J.B., V.C. interpreted the results. V.C. wrote the Article. All authors contributed to and approved the final version of the Article.

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4.3 Discussion

This study assessed the testing resources required to support reactive screening under high incidence conditions, as applied in France in early 2022. If reactive screening succeeded in reducing absences compared to reactive class closures implemented in Italy, it required a large number of tests with limited control. Weekly screening instead remained a more functional approach, using the same amount of resources as the reactive strategy while maintaining low absences and transmission levels.

The arrival of the Omicron variant in France prompted changes in the tracing and isolation procedures for positive students as part of an effort to adapt to the evolving pandemic. In December 2021, primary French schools introduced a reactive screening approach as outlined in Chapter 1. This approach aimed to achieve several objectives: 1) reduce the number of days students were unable to attend in-person classes; 2) lessen the burden of quarantine policies on students and families; 3) maintain a safe school environment; and 4) contain costs [184]. However, when schools reopened in January 2022 after the Christmas holidays, the sharp increase in COVID-19 cases among children led to an update of the reactive strategy. The new strategy, namely the strengthened reactive screening, included class-wide screening three times per week whenever a symptomatic student was diagnosed. By calibrating the model to the reported cases in children from the surveillance system, we showed that the reactive screening approach implemented in January 2022 failed to effectively control cases during the peak period. This ineffectiveness could be attributed to the inability of this approach to detect asymptomatic cases, which could have initiated transmission chains, especially among children who may not exhibit symptoms. Consequently, class screening often occurred too late to curb the spread effectively. Additionally, our findings showed that reactive screening, while saving school days compared to class closures, proved to be as expensive as weekly screening when there was a recurring importation of cases.

Field studies testing forms of reactive screening supported that reactive screening could facilitate school attendance with a similar or minimal increase in transmission compared to class quarantines. For example, during the Alpha wave in England (March-May 2021), voluntary daily contact testing was implemented for school-based contacts in nearly 200 schools [185]. A comparison between schools with contact tracing and those applying self-isolation of school COVID-19 contacts for 10 days revealed they were equally effective in controlling cases, with similar rates of symptomatic infections among students and staff. Similarly, in certain districts in North Carolina, US, during the circulation of the Omicron variant, serial reactive screening was implemented in schools where mask-wearing was optional [186]. Under this test-to-stay strategy, contacts were tested on the day of exposure notification, as well as three and five days after exposure. This approach allowed students and staff to remain in the classroom and resulted in moderate rates of subsequent infection among close positive contacts, ranging from 5% to 10%. At the same time, the study also acknowledged the challenges of implementing a test-to-stay program in high-incidence conditions, such as testing capacity limitations, resource availability, and difficulties in contact tracing when the number of cases to track became high. Moreover, both studies did not

allow for a direct comparison with weekly screening.

Through modelling, our study demonstrated that implementing weekly screening could prevent more cases compared to reactive screening. This was because weekly screening allowed for early detection of asymptomatic infections, both from external sources and within the school community, which could contribute to transmission if left undetected. Unlike the previous study presented in Chapter 3, we considered that weekly screening should be applied to 75% of the school population, regardless of their vaccination status. This adjustment was made because unvaccinated individuals were no longer the primary sources of transmission. Transmission due to reinfection or vaccination breakthrough was allowed with the Omicron variant, and screening efforts focusing only on the unvaccinated may result in less effective countermeasures [187].

Regarding acceptability of weekly screening, which was previously discussed as a potential barrier, interviews with early adopters of screening programs in the US during 2021 revealed that it instilled a sense of safety among staff and families that promoted the engagement [188]. A similar positive response was observed during the experimental weekly screening campaign conducted in the Auvergne-Rhône-Alpes region in France in December 2021, as discussed in Chapters 1 and 2. In fact, some primary schools participating in the campaign decided to continue weekly screening even after the Christmas holidays and the reopening of schools in January 2022. This decision was supported by families who wanted to avoid the disorder associated with reactive screening, which lacked a predetermined plan for testing children. On the contrary, weekly screening allowed for advance planning of who would be tested and when, thus avoiding potential burdens and shortages, as experienced during the peak of the Omicron variant. Therefore, while weekly screening may initially face challenges related to resource allocation, once implemented, it provided a more structured approach to control the viral spread, manage resources and limit absences.

The low vaccination coverage among children in Europe, due to delayed approval and rollout compared to other age groups, contributed to the overall burden of infections during the Omicron variant. Our research demonstrated that implementing vaccination would have reduced peak cases, although the effectiveness would have depended on the time interval since the last dose. Successive studies have shown that waning immunity occurs faster with the Omicron variant compared to previous variants [94, 189]. To address this issue and enhance protection, updated versions of vaccines that better match the circulating SARS-CoV-2 virus variants have been developed [190].

This study has some limitations. We considered a fixed participation rate of 75% for weekly screening based on observations from the field in the Basel canton [182]. However, participation levels may differ in other contexts and fluctuate over time. In the following Chapter, we will explore the results from experimental schools in the Auvergne-Rhône-Alpes region, where weekly screening was encouraged. While overall adherence was high, it varied in time ranging from 60% to 80% over six weeks of experimentation during the Omicron wave. Secondly, we did not address the logistical costs associated with implementing testing strategies. In some countries, the lack of economic resources may pose a significant obstacle to setting up testing programs. Notably, many screening initiatives,

both weekly and reactive, have been initiated in the United States, where national authorities allocated 10 billion dollars in support [191]. Consequently, schools in under-resourced communities may face resource constraints, which force them to use class closure. Thirdly, this study focuses exclusively on the school setting and can not evaluate the impact on households and the broader community. Studies on the spread of the SARS-CoV-2 Alpha and Delta variants found that in-person schooling, without multiple mitigation measures, increased the risk of COVID-19-related outcomes among family members, despite high vaccination rates in adults [192]. Similarly, studies conducted in Geneva [193] and South Korea [194] suggested that children could serve as a source of infections within households and beyond during the Omicron variant spread.

In our study, we have shown the importance of incentivizing non-pharmaceutical interventions, particularly when vaccination rates are low, as observed during the Omicron wave in Europe [178]. We showed that both weekly and reactive screenings required significant resources under high-incidence conditions. However, the main difference lay in the fact that weekly screenings offered a safer approach to facilitating in-person education compared to reactive ones and as an alternative to class closure. The findings allowed policymakers to update guidelines based on evidence, especially if the decision to implement reactive screening was made with the intention of saving resources compared to weekly screening. In situations where resources were limited, it would have been advantageous to develop and implement flexible programs that enabled schools to adjust testing strategies based on the risk of COVID-19 transmission, as additionally supported in a later study set in the US [195]. Regular screening tests would have helped identify and contain outbreaks when viral spread was significant. Instead, a reactive program following a symptomatic diagnosis would have allowed to manage test costs efficiently as the risk decreased.

In conclusion, this work emphasized the importance of considering multiple cost dimensions in school policies and recommended a long-term dynamic strategy. This approach enabled schools to potentially move to screening regimens in high-incidence conditions, informing and optimizing resource requirements if limited, facilitating in-person learning, and aligning control measures with specific needs.

Investigating the role of school transmission during the 2021/2022 winter Delta and Omicron waves

In this Chapter, I will present an ongoing work in which I retrospectively investigate the degree of in-person COVID-19 transmission in schools and the extent to which weekly screening averted school transmission during the Delta and Omicron waves. I use student prevalence data collected in the field and the methodological framework developed in the previous Chapters to fit the model to these data. For the Omicron period, I also include a dynamic vaccination rollout. The study allows us to measure the effectiveness of the weekly screening from a real-world experiment and offer empirical evidence to provide better-tailored guidelines in the future. The manuscript contained in this Chapter is currently *in preparation*.

5.1 Introduction

In the previous Chapters, I presented numerical evidence supporting the effectiveness of weekly screening. This evidence influenced the French authorities to trial a weekly screening regimen in selected primary schools in the Auvergne-Rhône-Alpes region [72]. The trial took place between December 2021 and February 2022, coinciding with the Delta and Omicron waves. These periods witnessed a concentration of SARS-CoV-2 spread among children, who had lower vaccination rates compared to other age groups, as discussed in Chapter 4. The objective of this study is to quantify the risk of transmission among school contacts, specifically concerning the more transmissible Delta and Omicron variants when implementing weekly screening. The ultimate goal is to provide insights that validate the effectiveness of weekly screening in place of the national reactive screening under the conditions experienced during the Delta and Omicron waves. The extended time frame covered by the data collected during the experimentation compared to those from the Alpha period (Chapter 3, Article #1) enables a more comprehensive understanding of the impact of the weekly screening on the transmission dynamics in school. To achieve the objectives outlined, we use the student prevalence data collected during the experimental weekly screening and an adjusted version of the previously developed mathematical model.

5.2 Article #3: Estimate of COVID-19 school transmission contribution during weekly screening in the Auvergne-Rhône-Alpes region, France, week 47, 2021 to week 06, 2022

Estimate of COVID-19 school transmission contribution during weekly screening in the Auvergne-Rhône-Alpes region, France, week 47, 2021 to week 06, 2022

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Abstract

Reactive screening strategies were applied nationwide in France in late 2021 in response to the winter Delta and Omicron waves. In the same period (week 47 to 50, 2021 and week 01 to 06, 2022), an experimental weekly screening protocol was proposed in 25 primary schools in the Auvergne-Rhône-Alpes region to early identify and isolate cases and avoid further transmissions. Here, we estimate the impact of the experimental protocol in terms of school transmission and reduction of school-related infections, compared to the national reactive protocols. We extended an agent-based model for SARS-CoV-2 transmission over a temporal contact network composed of teachers and primary school students [1]. We parametrized the model to reproduce the Delta and Omicron variants dominant in the study period, accounting for introductions from community surveillance data. We then fitted the model to the observed prevalence in the 18 schools selected for the analysis.

We estimated a relative contribution of school transmission compared to the introduction of 67% (IQR 53-78) in the Rhône department and 67% (IQR 50-82) in the Savoie department under the Delta period, and 52% (IQR 47-57) in the Rhône department during the Omicron wave. The reduction in school transmission achieved by the experimental protocol was estimated to be 40% (IQR 18 - 53%) over the first four weeks of experimentation and 37% (IQR 30-45) over the second six weeks compared to the reactive strategies applied nationwide. Through field estimates, these findings confirm previous model predictions anticipating the effectiveness of systematically screening the school population to reduce the number of school-related infections. They also provide key information to improve the design and implementation of school-based strategies for pandemic preparedness plans.

INTRODUCTION

For the school year 2021-2022, a tiered system composed of four levels was developed in France by the Ministry of Education to provide guidelines in terms of attendance, sanitary measures, physical distancing, and contact tracing at school based on the epidemic activity [2]. The system aimed to maximize in-person teaching in order to preserve the well-being of students while limiting the circulation of the virus within schools. The stringency of sanitary and physical distancing measures increased with levels and aimed mainly at reducing person-to-person transmission and exposure through limited mixing between students of the same grade or classmates during lunch or sports activities, face mask wearing, etc. In continuation with the previous academic year, class closure was adopted as a contact tracing strategy since classmates were considered to be at high risk of exposure. However, with the emergence of the Delta wave in Fall 2021, class closures became increasingly frequent, affecting almost 2% of French classes on November 26, 2021, with 73 out of 48,950 primary schools completely closed [3]. To limit educational disruption for individuals who did not require isolation, reactive screening strategies were proposed nationwide in France as an alternative to class closure starting from week 49 of 2021 (06/12/2021) [4]. With the new protocol, in-person attendance was ensured through class screening upon the identification of a first case. In this way, only students testing positive had to stay in isolation, and forced quarantine for the other classmates was

avoided. At the same time, increasing model-based evidence started to promote systematic screening of the school population on a weekly or semi-weekly basis as a more effective control strategy compared to class closure or reactive screening [1], [5], [6]. Systematic screening could proactively identify all possible forms of infection (symptomatic or asymptomatic) and promptly interrupt transmission chains. On the contrary, reactive strategies were predicted to poorly affect ongoing transmission because they were only activated in response to a symptomatic case. Therefore, all asymptomatic cases that occurred before or after the identification of a case were likely missed. For this reason, French authorities decided to experiment with a weekly screening regimen in voluntary primary schools in the Auvergne-Rhône-Alpes region from week 47 of 2021 to week 50 of 2021[7]. The objective of the experimentation was to examine the effectiveness of weekly screening in minimizing transmissions among children in a real-world situation by monitoring student prevalence.

In this work, we used a stochastic model and field screening data to estimate the role of school transmission and the expected case prevention due to the experimental weekly screening compared to national reactive strategies during the winter Delta and Omicron waves.

METHODS

Data collection under the experimental weekly screening

The experimental screening campaign was targeted to students of 25 selected primary schools (students aged 6-10 y.o) in the departments of Isère, Puy-de-Dôme, Rhône, and Savoie in the Auvergne-Rhône-Alpes region. The campaign was conducted over two periods separated by the Christmas holidays: the first round spanned week 47-50, 2021 (22/11/2021-17/12/2021), and the second round took place during week 01-06, 2022 (03/01/2022-13/02/2022). The first round was performed during the Delta wave (>99% of Delta variants detected in week 43, 2021) characterized by peak incidence values of 1,457 per 100,000 cases in the age class 6-10 y.o. (week 49, 2021), whereas the second round of screening was carried out during the Omicron wave (96% of BA.1 Omicron variant detected in week 02, 2022) with peak incidence values of 7,652 per 100,000 cases (week 03, 2022) in the age class 6-10 y.o. (**Figure 1**).

The objective of the experimentation was to collect student prevalence data and, through that, assess the effectiveness of the weekly screening in terms of case prevention.

Over the course of the experimental weekly screening (week 47, 2021 – week 06, 2022), self PCR tests on saliva samples were proposed to the students in primary schools on a voluntary basis every Monday. Screening for SARS-CoV-2 was conducted jointly by medical laboratories and schools. The school principals provided lists of classes and participating students to the assigned laboratories. Informed written consent was obtained from the parents of the students. Each laboratory was responsible for scheduling the tests and communicating the results. During each round, students performed a weekly self-sampling test for SARS-CoV-2 using saliva samples at home before attending school. Molecular testing was required to confirm a positive case identified through saliva samples. Students who tested positive were required to isolate themselves for 7 days, and their positive status was reported to local health authorities for further investigation. If more than 3 positive cases of SARS-CoV-2 were identified within the same class, the entire class would be closed for a period of 7 days. Data on the number of students present on the screening day, the number of tests conducted, and the number of positive cases were collected.

For the analyses, we selected only those departments with at least 5 screened schools per week (which was equivalent to considering the departments with ≥ 500 tested students per week). During the first round, 9 primary schools with 7,434 tested students met the reference inclusion criteria in the Rhône department and 8 primary schools with 2,863 tested students in the Savoie department. For sensitivity analysis, we removed the constraint on the number of screened schools and considered the totality of schools that decided to adhere to the experimentation, resulting in an additional 5 primary schools with 3,103 tested students in the Isère department and 2 primary schools with 1,230 tested students in Puy-de-Dôme. For the second round, 10 primary schools with 13,143 tested students met the reference inclusion criteria in the Rhône department. No sensitivity analysis was performed since some departments decided to discontinue experimentation in 2022 or to interrupt it earlier. The number of tests performed by week and department is reported in **Table 3**.

For each screening week and department, adherence was computed as the ratio between the overall number of tested students and the overall number of students present on the day of the screening (**Table 4**). Analogously, we computed the prevalence as the ratio between the overall number of positive tests and the overall number of students tested on the day of the screening. The observed prevalence at school is reported in **Table 5**.

Nationwide school protocols

In the time interval between week 45 of 2021 and week 06 of 2022, two changes in school protocols nationwide occurred. The reactive class closure strategy upon detection of a first case was applied nationwide up to week 48, 2021. According to this protocol, positive cases and classmates had to be isolated for 7 days. To face the Fall Delta wave, reactive screening strategies were applied in place of reactive closure starting from week 49, 2021 [4], [8]. Under this strategy, all the students in the same class of a case were invited to perform a RT-PCR or later-flow device (LFD) test after 1 day (d1) and after 7 days (d7) from the detection of the first symptomatic case. Only students with a proven negative test were allowed to attend in-person lessons, while others were required to isolate for 7 days. Quarantine for positive cases lasted 10 days. The appearance of three confirmed cases among students led to the closure of the classroom for 7 days.

A strengthened version of the reactive screening strategy was promoted at the beginning of January 2022 after the emergence of the Omicron variant. The strengthened reactive screening required an LFD or RT-PCR test at day 0 (d0), followed by 2 self-tests on days 2 (d2) and 4 (d4) from the detection of a symptomatic case for the students in the same class. Students with a positive test were put in isolation for 7 days. Tests were carried out by families at pharmacies, laboratories, or similar structures, not necessarily in schools. A self-test at day 0 was also accepted as an alternative to an LFD or RT-PCR test on January 14, 2022 [9]. No class closure was required. However, local authorities could decide to employ it if there were a high number of cases.

Transmission model

We used a stochastic agent-based model already developed to study the Alpha wave in school settings [1] to simulate the spread of SARS-CoV-2 over an empirical school contact network composed of 232 primary students and 10 teachers divided into 10 classes [10]. Contacts were defined as face-to-face proximity interactions and were captured through RFID sensors with a time resolution of 20 seconds. On average, children were found to have a higher number of distinct contacts during a day, interacting with nearly all of their classmates (83% of the class). Inter-class links were approximately 50% more frequent than intra-class links. When accounting for the duration of interactions, children spent more time on average interacting within their own class than outside the class, and the contact duration they established was 64% longer compared to the contacts established by teachers.

Within the school, transmission could occur between close contacts as specified by the school contact network. For susceptible individuals, the probability of acquiring the infection was proportional to the transmission rate per contact β , their own susceptibility, and the duration of the contact. The transmission rate β was calibrated to reproduce the observed student prevalence (see Inference framework section). Susceptibility and transmissibility differed between students and teachers, as the propensities to get or transmit the infection were estimated to increase with age [11], [12]. In the main analysis, students were assumed to be 50% as susceptible as teachers [13] and 63% as infectious as teachers [14]. Students also had a reduced probability of showing symptoms [12], [15]–[17] and to be detected as symptomatic cases compared to teachers [18], [19].

Once infected, the epidemiological state of each individual in the school network evolved through the prodromic stage, the symptomatic or asymptomatic stage, the recovered but detectable stage, and the fully recovered stage. Stages were informed by empirical distributions [20]–[22].

We extended the model introduced in [1] to reproduce the epidemiological characteristics of the Delta and Omicron variants. Students who had fully recovered from previous variant infections had a 40% probability

of being reinfected upon exposure to the Omicron variant [23]. We assumed the same probability of reinfection for teachers in the network.

Furthermore, we stratified the model by assigning a vaccination status to each individual, distinguishing between unvaccinated, fully vaccinated, and boosted individuals. We defined fully vaccinated individuals as those who completed the primary vaccination course consisting of two doses. Individuals with a third shot were defined as boosted individuals [24]. Vaccinated individuals had a reduced susceptibility, transmissibility, and probability of developing symptoms thanks to the protection provided by the vaccine. The vaccine effectiveness (VE) against infection, symptomatic infection, and transmission depended on age, the number of doses received, the time from the administered doses, and the variants.

During the Delta period (week 45 – week 50, 2021), we considered that 90% of teachers were fully vaccinated and 10% were boosted according to the coverage reported in the national registers (reference age class 18-59 y.o.) [24] while no vaccination was considered for children as they were not eligible until 22 December 2021 [25]. Since vaccination for teachers opened in May 2021 [26], we considered estimates for VE after 3-6 months from the primary vaccination course, i.e. 64% against infection, 71% against symptomatic infection, and 25% against transmission [27]. The booster campaign for the adult population began in late November 2021 in France [28]. Therefore, we used VE estimates corresponding to the first 9 weeks after the booster shot. In particular, we considered 82% against infection, 91% against symptomatic infection and 50% against transmission [27], [29].

In January 2022, vaccination in children started slowly progressing in France, reaching 3% coverage by week 06, 2022 [24]. The rollout for adults was much faster, with 60% of the population in the age bracket 18-59 having received the booster dose by week 06, 2022 [24]. The first evidence on children's VE during the Omicron variant surge in the US showed a rapid decline in the protection conferred by the vaccine over time since full vaccination [30]. We therefore considered a dynamic vaccination status for both students and teachers during the Omicron period. Every week, a percentage of students and teachers was randomly selected, and their vaccination status was updated to fully vaccinated or boosted individuals. The selected percentage of students and teachers reflected the weekly vaccination coverage recorded in that period in the corresponding age class (5-11 y.o. for students and 18-59 y.o. for teachers) in France [24]. Vaccine effectiveness evolved according to the observed waning against the Omicron variant and the time elapsed since vaccination. For children, VE against infection ranges from 65% immediately after having completed the primary course to 12% after 1 month [30]. In the absence of data, we considered VE against transmission in adults after 2 doses. In adults, VE values remained more stable over time but were lower compared to the Delta variant. When fully vaccinated, the effectiveness against symptomatic infection was 17% after 3-6 months since vaccination and 64% after 1-9 weeks from the booster dose.

Simulations

We simulated school protocols depending on the weeks under study in line with the protocol's evolution illustrated in **Table 1**.

Table 1. Timeline of the school protocol's evolution between week 45, 2021 and week 06, 2022.

Study period	week	where	protocols	isolation	test	turnaround
1	45-46, 2021	Nationwide	Reactive class closure	Confirmed symptomatic cases have to isolate for 7 days. All the classmates are put in quarantine for 7 days	Salivary PCR	1 day

	47-50, 2021	Only in schools adhering to experimental weekly screening	Weekly screening	Positive cases identified through screening or symptomatic testing have to isolate for 7 days. The appearance of three confirmed cases among students led to the closure of the classroom for 7 days.	Salivary PCR	1 day
2	01-06, 2022					

In weeks 45 and 46 of 2021, before the introduction of experimental weekly screening, we simulated the reactive class closure adopted nationwide in France, implying the closure of the class for 7 days after the identification of a case. Starting from week 47 to week 50 of 2021, we simulated the weekly screening program on students as applied in the experimental schools considering the observed adherence. Students who tested positive underwent 7 days of isolation. If more than 3 positive cases appeared in the same class, reactive class closure was activated.

For the Omicron analysis, only experimental weekly screening was simulated as illustrated in **Table 1**.

For simplicity, we considered salivary PCR tests for all the simulated protocols and a turnaround time of 1 day. Test sensitivity was assumed to be age-dependent and time-varying. Salivary PCR tests were assumed to be as sensitive as nasopharyngeal PCR tests. The peak test sensitivity was estimated to be 96% [31].

Age-specific seroprevalence estimates and vaccination coverage were used to inform and initialize the model [32], [39]. Weekly introductions were stochastically estimated using age-specific community surveillance data by department and adjusted to account for detection rate and estimated within-school transmission. The starting week of each simulated period coincided with the reopening of schools following two weeks of holidays, during which transmission chains within schools were assumed to be interrupted.

Inference framework

We used a maximum likelihood estimation (MLE) approach to fit the model to the student prevalence observed in the primary schools with the experimental weekly screening in place. We estimated the transmissibility per contact per unit time (β/min) at school for the Delta and Omicron variants. We considered time-varying adherence based on the observed participation rate in the experimental screening for each department.

The detection rate in the community was a free parameter changing before and after the implementation of the experimental protocol during the Delta wave (weeks 45-50, 2021). It was explored in a grid and selected using the Akaike Information Criterion (AIC) score.

During the Omicron phase (week 01 – week 06, 2022), the detection rate was estimated by comparing surveillance community data for the age class 5-11 y.o. and reported prevalence at school.

Transmissibility estimates during the Delta and Omicron periods were obtained from 2000 simulated stochastic outbreaks for each parameter set over a 6-week period (42 days). For sensitivity analysis, we also explored the impact of cohorting and a lower test sensitivity in the asymptomatic group in the pre-symptomatic and post-symptomatic phases.

Effectiveness of weekly screening

Assuming the estimated transmissibility β_{MLE} and weekly introductions, we simulated a counterfactual scenario, introducing the protocols adopted nationwide to measure the effectiveness of the experimental weekly screening in preventing infections at school.

More in detail, from weeks 45 to 48 of 2021, we simulated the reactive class closure, implying the closure of the class for 7 days every time a positive student was found. From weeks 49 to 50 of 2021, we simulated the reactive screening, requiring a test for the students in the same class of a case after 1 day and 7 days from the detection. Positive cases were put in isolation for 7 days. Whenever 3 positive cases appeared within a week, a reactive class closure was triggered. The participation rate within a class was fixed at 68%, corresponding to the median adherence observed under the experimental weekly screening. From week 01 to week 06 of 2022, we simulated the strengthened reactive screening. Students in the same class of a confirmed case had to perform a test on the day of detection and, 2 days, and 4 days later. Isolation for positive cases lasted 7 days. No class closure was required.

Table 2. Additional school protocols simulated as a counterfactual scenario by weeks.

Study period	Week	where	protocols	isolation	test	turnaround
1	45-48, 2021	Nationwide (except for the schools participating to the experimental weekly screening from week 47)	Reactive school closure	Confirmed symptomatic cases have to isolate for 7 days. All the classmates are put in quarantine for 7 days	Salivary PCR	1 day
	49-50, 2021	Nationwide (except for the schools participating to the experimental weekly screening)	Reactive screening after 1 and 7 days from the symptomatic case detection	Positive cases identified through screening have to isolate for 7 days. The appearance of three confirmed cases among students led to the closure of the classroom for 7 days. Students not compliant to screening have to stay in quarantine for 10 days	Salivary PCR	1 day
2	01-06, 2022	Nationwide (except for the schools participating to the experimental weekly screening)	Reactive screening at d0, and after 2 and 4 days from the symptomatic case detection	Positive cases identified through screening have to isolate for 7 days.	Salivary PCR	1 day

RESULTS

A total of 28,643 tests were performed at school between week 49 of 2021 and week 06 of 2022 (3,653 in Isère, 1,230 in Puy-de-Dôme, 20,577 in Rhône, 3,183 in Savoie), with 1,001 positive results (54 in Isère, 11 in Puy-de-Dôme, 880 in Rhône, 56 in Savoie). **Figure 1** shows the number of schools involved over time by departments. The number of tests, the observed adherence, and the prevalence are reported in **Table 3**, **Table 4**, and **Table 5** respectively.

Table 3. Number of tests by weeks and departments in the primary schools participating in the experimental weekly screening.

	1 st Round				2 nd Round					
Departments	W47	W48	W49	W50	W01	W02	W03	W04	W05	W06
Isère	468	916	935	784	398	152	/	/	/	/
Puy-de-Dôme	337	299	311	283	/	/	/	/	/	/
Rhône	1369	1847	2111	2107	1769	2246	2514	2503	1827	2284
Savoie	537	692	804	830	/	49	67	79	70	55

Table 4. Observed adherence by weeks and departments in the primary schools participating in the experimental weekly screening.

	1 st Round				2 nd Round					
Departments	W47	W48	W49	W50	W01	W02	W03	W04	W05	W06
Isère	58.2	61.8	64.7	52.9	60.4	55.1	/	/	/	/
Puy-de-Dôme	73.9	65.7	68.7	63.2	/	/	/	/	/	/
Rhône	69.7	68.1	81.5	82.1	71.3	74.3	83.6	81.9	59.5	74.3
Savoie	58.9	65.1	75.4	68.4	/	48.0	48.5	52.3	62.5	50.5

Table 5. Observed prevalence points by weeks and departments in the primary schools participating in the experimental weekly screening.

	1 st Round				2 nd Round					
Departments	W47	W48	W49	W50	W01	W02	W03	W04	W05	W06
Isère	0.85	0.33	2.67	0.13	5.28	0.00	/	/	/	/
Puy-de-Dôme	0.89	2.00	0.64	0.00	/	/	/	/	/	/
Rhône	1.53	2.33	1.33	0.95	5.03	8.06	8.15	5.07	5.09	3.20
Savoie	1.30	2.17	2.24	0.96	/	0.00	1.49	6.33	2.86	0.00

Figure 2A and **Figure 2C** show the predicted student prevalence at school, obtained with the maximum likelihood estimate of the transmissibility β_{MLE} per contact compared to the observed prevalence during the first round of experimentation in the departments selected through the inclusion criteria. The detection rates that best reproduced the observations were $p_{d1} = 70\%$ when reactive class closure was in place, and $p_{d2} = 100\%$ during the first round of experimentation. **Figure 2B** shows the same for the second round of experimentation. Here, the estimated detection rate was $p_d = 93\%$.

To evaluate the within-school transmission contribution, we estimated the total number of student cases, distinguishing school-related ones from community introductions. During the first round of experimental weekly screening, we estimated that 12 (IQR 8-18) and 10 (IQR 6-14) infections were generated in a primary school of 232 students in the Rhône and Savoie departments in 4 weeks (**Figure 3 A**). The relative contribution of school transmission was predicted to be 67% (IQR 53-78) in the Rhône department and 67% (IQR 50-82) in the Savoie department (**Figure 3 C**). During the second round of experimental weekly screening, 49 (IQR 43-55) infections were estimated to be associated with school transmission in a primary school of 232 students in the Rhône department (**Figure 3B**). The relative contribution of school transmission was 52% (IQR 46.7-56.4) (**Figure 3D**). The estimated relative contribution remained relatively stable when considering a longer stay in the post-symptomatic compartment R_+ (10 days instead of 6 days), the cohorting, or a lower test sensitivity for the pre-symptomatic, asymptomatic, and post-symptomatic phases.

To estimate the effectiveness of the experimental protocol compared to the one adopted nationwide, we computed the prevalence that the schools under national reactive strategies would have experienced assuming the same number of introductions during the study periods. The reactive screening strategy adopted in week 49 of 2021 and substituting the reactive quarantine was estimated to result in a student prevalence peak equal to 3.0% (IQR 1.9-4.6%) and 2.1% (IQR 1.1-3.5%) for the Rhône and Savoie departments, respectively. Under the reactive screening, the peak student prevalence was estimated to be 1.5 and 1.3 times higher compared to the peak reached by the weekly screening. (**Figure 4A, C**). We estimated that the percentage of averted school transmission achieved by weekly screening under the first round was 39.5% (IQR 18.4-53.3%) compared to the nationwide reactive strategies applied in the same time interval (**Figure 4D**). The strengthened national reactive screening (d0, d2, d4) applied in the weeks 01 to 06 of 2022 was estimated to result in a peak prevalence of 11.7% (IQR 9.4-14.1), i.e., 1.4 higher compared to the peak associated with the experimental weekly screening. (**Figure 4B**). The percentage of school transmissions averted by weekly screening compared to the strengthened reactive strategy was 37.2% (IQR 29.5 - 44.9%) (**Figure 4D**).

DISCUSSION

Using field screening data collected during an experimental weekly screening in the Rhône and Savoie departments during the Delta and Omicron waves, we estimated the within-school transmissibility for each wave. Our results predicted that a significant proportion of COVID-19 cases in children were related to school contacts. The school contribution was larger in the Delta wave (ca 67% of student infections occurred at school) than in the Omicron wave (ca 52% of student infections occurred at school), during which a higher number of introductions contributed to the overall number of infections. Finally, we estimated that the benefit of the experimental weekly screening with respect to the national reactive screening strategy was ca 40% in the Delta wave and ca 39% in the Omicron wave.

A decline in student prevalence was observable under the weekly screening regimen. Interestingly, this decline in student prevalence occurred 1 week before the estimated peak prevalence reached by reactive strategies. This suggested a decrease in viral circulation among children as a result of the weekly screening implementation (1-2 weeks after the start of experimentation). Higher participation rates in the last two weeks of the first round of experimentation (>80% in Rhône, >67% in Savoie) compared to the start contributed to flattening the prevalence curve. Similar trends could also be identified in the second round of experimentation, with a decay in the student prevalence after the peak adherence was reached (>80% in Rhône in weeks 03 and 04 of 2022).

Our results showed a considerable contribution by the school as a source of children's infections during the Delta and Omicron periods. The lower percentage estimated during the second round, when the Omicron variant was circulating, suggested a higher viral circulation in the community, possibly related to the transmissibility advantage or immune evasion properties of this variant compared to the Delta one. Recent outbreak investigations have evidenced the extent of child and school transmission during the Alpha wave [32], [33]. In the first study, it was estimated that when the Alpha variant was circulating and a systematic screening was in place in Liège in Belgium ca 66% of transmissions originated at school, and most of the direct transmissions occurred between children or from children to adults. This is in line with the results obtained from another school outbreak investigation in Emilia Romagna, northern Italy, during the Alpha wave. Under the reactive quarantine policy, the study estimates that nearly half of the confirmed cases among school attendees acquired the infection from a school contact [33]. Our study thus provides additional insights into the school contribution with the more transmissible Delta and Omicron variants that support the role of school contacts in transmission.

We showed that weekly screening was more effective than reactive screening as it enabled the identification of a higher number of cases, including pre-symptomatic and asymptomatic ones that would otherwise go unnoticed while unknowingly contributing to disease spread. Indeed, we found that approximately 50% of cases identified through screening were asymptomatic in both study periods. Different field initiatives were set up in Europe to determine whether children were less likely to get the infection at school or were simply less likely to be identified without systematic screening because they were asymptomatic. In the COVID-19 Schools Infection Survey conducted in England over the years 2020–2021, the majority of cases found through student screening were asymptomatic [34]. Another screening

campaign experimented in the region of Piedmont (northern Italy) in January-March 2021 targeted to the students of the second and third grades of first-level secondary schools (11-13 y.o.), found that asymptomatic cases accounted for ca 27% of the total number of cases when the spread in the community was relatively high [35]. Our results confirm previous model predictions showing the effectiveness of weekly screening in reducing the number of school-related infections due to asymptomatic transmission among the school population [6], [36], [37].

We showed that the reactive screening applied in France in late December 2021 was not able to control the number of infections in schools and led to higher percentages of student prevalence compared to the use of proactive protocols. Strengthening the reactive screening by increasing the frequency of tests and shortening the time interval between screenings in response to the Omicron wave did not prevent a large peak of cases (estimated peak prevalence under reactive d0, d2, d4, ca 12%) compared to weekly screening. Besides poor control, reactive screening strategies came with a rapid surge in test demand when solicited by the continuous occurrence of COVID-19 cases [38]. Moreover, the reactive screening approach was subordinated to the presence of at least one confirmed case for its activation, lacking predictability. This, in turn, complicated resource allocation. The uncertainty surrounding when and where the next cases might emerge added stress and anxiety to teachers and parents. In France, teachers expressed concern about returning to school with the strengthened reactive in place during the Omicron wave, and they were worried about the impact of this protocol on their job and the children's learning continuity [39]. Moreover, families faced considerable difficulties in finding timely testing options because of the pressure on pharmacies and laboratories associated with the high testing demand. Without a negative test, children had to stay at home, which in turn implied time off from the office for parents. Instead, a proactive approach to screening represented a more organized and structured strategy from many points of view, such as logistics, school management, and families. However, according to the second round of the UNESCO-UNICEF-World Bank survey on National Education Responses to COVID-19 School Closure conducted between May and August 2020, only 19% of countries declared to plan testing for COVID-19 at the school level, while only 50% of low and middle-income countries said to have enough resources to implement even the more basic health and hygiene protocols [40]. In case of a new pandemic crisis in the future, this means that more economic investments from governments need to be considered to support systematic screening. On the other hand, in cases of limited resources, pooled screening or a more relaxed frequency of screening can help control resources and costs. A modeling study investigating the problem of optimal test allocation in the context of COVID-19 suggests a criterion based on school and community transmission risk to decide whether and how to distribute resources while reducing infections across different regions [41].

Our study has some limitations. First, we did not assess the airborne contribution to the viral circulation and how ventilation measures could help in controlling the transmission at the time of experimentation, as we mainly modelled the transmission by close contacts. During the first round of the experimental weekly screening in France, 93.1% of the schools declared to apply classroom natural ventilation more than twice per day, and masks were compulsory. Modelling studies integrating epidemiological, environmental, and molecular data collected in schools in Switzerland revealed that mask mandates could greatly reduce aerosol concentration and, consequently, lessen transmission associated with this route [42]. In a retrospective cohort study conducted in primary schools in the Marche region of Italy, mechanical ventilation was found to be associated with a 74% reduction in the relative infection risk for students in classrooms with mechanical ventilation compared to those in classrooms with only natural ventilation [43]. Therefore, mechanical ventilation, if in place, can additionally contribute to reducing the concentration of aerosol particles and droplets. Although reactive screening was experimented in 10 departments of France before its implementation at the national level [44], a direct comparison with weekly screening was not possible since the two time periods were different (the experimentation of reactive screening ended on November 26, 2021, just 4 days after the beginning of experimental weekly screening). By assuming the same number of introductions, our model enabled us to compare the reactive (and strengthened) protocol with the experimental weekly screening in terms of student prevalence. Third, we could not assess if weekly screening at school reduced transmission to households since our network of interactions was limited to school settings. However, in a case-control study conducted in France between May and August 2021 in correspondence with the emergence of the Delta variant, it was found that in the absence of school strategies, adults with school-aged children had a higher probability of getting the infection, suggesting that children could act as the seed of the infection. [45]. With more active surveillance in schools, we expect

therefore a lower risk of importations in other settings, such as households, and then to the community. Finally, we did not assess the effect of school size or school type as the experimental protocol was limited to primary schools only. More investigations are needed in this direction to well characterized the role of adolescents and the impact of vaccination since that the vaccination coverage was higher in this age class than in children. Our previous modeling work [1] showed that weekly screening would still be the most effective protocol compared to reactive strategies in high schools.

Although COVID-19 was declared no longer a global threat in May 2023 by the World Health Organization [46], understanding the role of schools and children in the spread of respiratory viruses is still crucial to controlling them. COVID-19 highlighted that school closure is not sustainable in the long term, despite the crisis to be managed. Schools were identified as one of the relevant operational topics for an after-action review of the public health response to COVID-19 [47]. Systematic screening can represent a valid option to contrast the pre-symptomatic and asymptomatic spread and guarantee safe access to education when highly transmissible variants are circulating. Our findings can thus be used to improve the design of non-pharmaceutical interventions in specific settings and inform future pandemic preparedness plans to make schools more resilient in the event of a pandemic crisis in the future.

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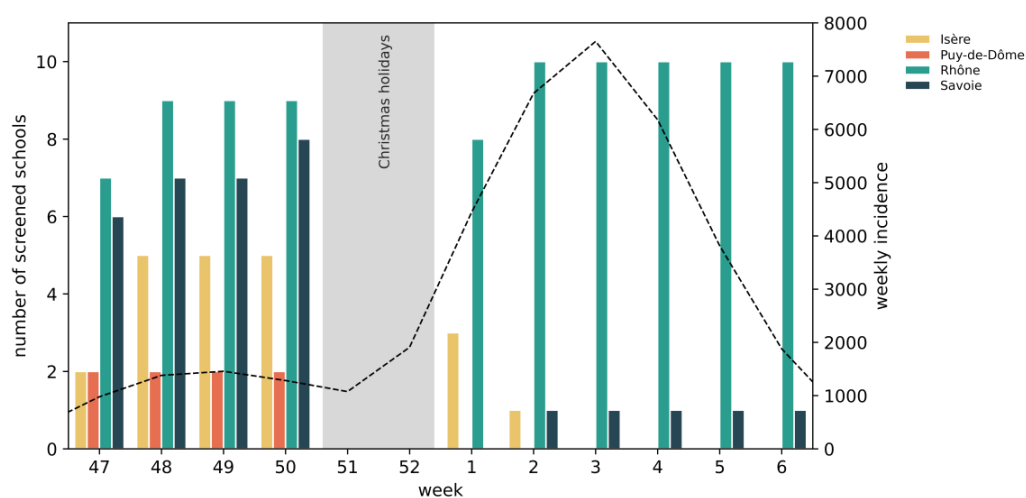


Figure 1. Number of screened schools and epidemiological situation in the four selected departments over the weeks from 47, 2021, to 06, 2022 (22/11/2021-13/02/2022). Number of screened schools for each department (solid bars) between week 47, 2021 and week 01, 2022. The four selected departments are: Isère, Rhône, Puy-de-Dôme, and Savoie. The dashed line indicates the weekly incidence (cases per 100,000) from community surveillance in the four selected departments for the age class 6-10 years, i.e., primary school students [24]. In light grey Christmas holidays (weeks 51-52, 20/12/2021-02/01/2022).

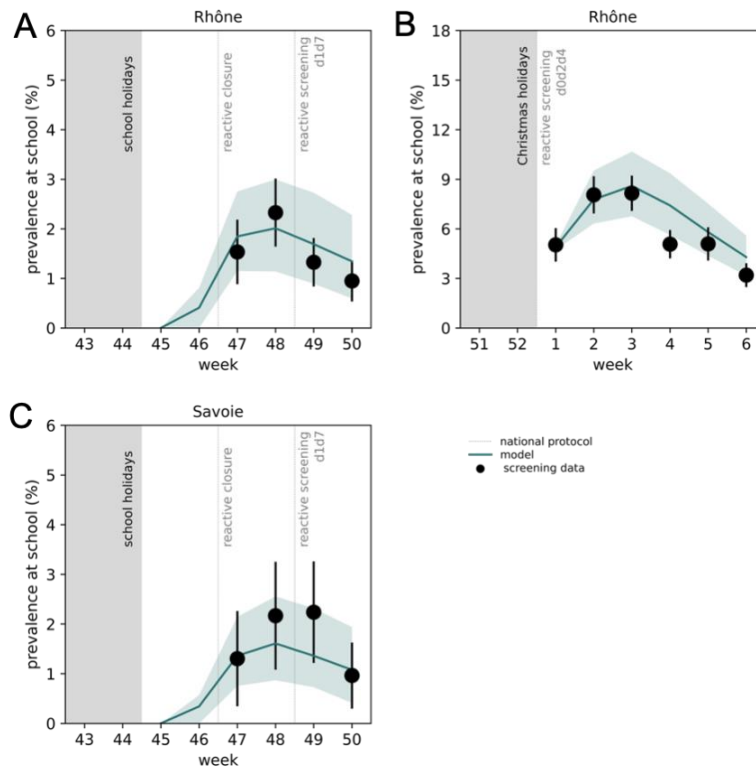


Figure 2. Estimated and observed prevalence at school during the first and second rounds of experimental weekly screening in the Rhône and Savoie departments. **A.** Green line represents the prevalence estimated by the model during the first round of experimentation during the Delta wave in the Rhône department selected through the inclusion criteria. The green area represents the interquartile range (IQR). The black dots represent the observed prevalence at school as obtained by experimental screening data. The error bars represent 95% confidence intervals. The grey area corresponds to holiday periods. Dashed grey lines show the protocols in place at the national level **B.** As in **A** for the Rhône department during the Omicron period. **C.** As in **A** for the Savoie department for the Delta period. In panels **1A** and **1C**, the simulated school protocols were reactive class closure from week 45 to week 46, 2021 and experimental weekly screening from week 47 to week 50 of 2021. In panel **1B**, the simulated school protocol was the weekly screening from week 01 to week 06 of 2022. In all the panels, we considered salivary PCR tests.

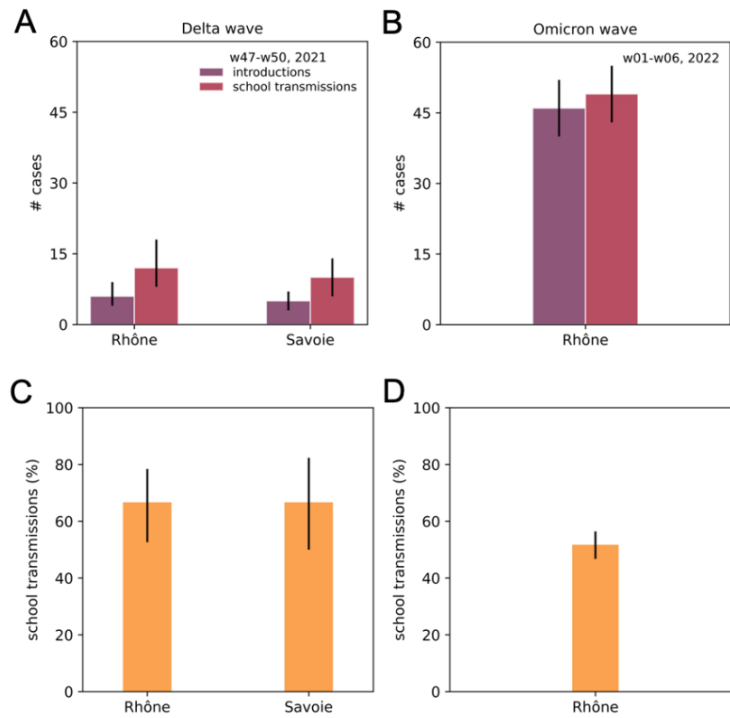


Figure 3. Predicted number of cases in students and estimated school transmission contribution during the first and second rounds of experimental weekly screening under the Delta and Omicron waves by departments. A: Bars show the absolute number of cases predicted by the model, distinguishing introductions (purple) from school transmissions (red) in the selected departments of Rhône and Savoie in the weeks of the first round during the Delta wave. The error bars in black represent the interquartile range (IQR). **B.** As in A during the Omicron period. **C.** Bars show the school transmission contribution predicted by the model in the selected departments of Rhône and Savoie in the weeks of the first round of experimentation during the Delta wave. The error bars represent the interquartile range (IQR) **D.** As in C during the Omicron period.

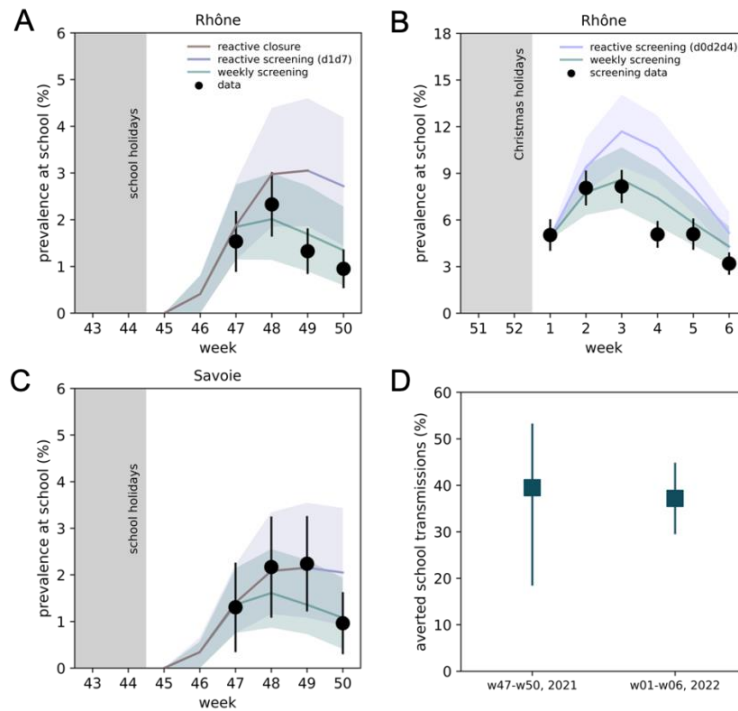


Figure 4. Comparison between estimated prevalence under the experimental weekly screening and the national reactive strategies by departments and estimated averted school transmissions. **A:** Lines represent the prevalence estimated by the model in the Rhône department across various school protocols: reactive class closure from week 45 to week 47 (brown line), reactive screening (d1d7) from week 49 to week 50 (violet line), and experimental weekly screening from week 47 to week 50 of 2021 (green line). Areas represent the interquartile ranges (IQR). The black dots represent the observed prevalence at school as obtained by experimental screening data. The error bars represent 95% confidence intervals. **B:** As in A during the Omicron period with the strengthened reactive screening (d0d2d4) at the national level from week 01 to week 06 of 2022. **C:** As in A for Savoie department. **D:** Percentage of averted school transmissions achieved by weekly screening compared to the reactive strategies in the two periods of experimentation. Test type: salivary PCR

5.3 Discussion

This study provides an estimate of the contribution of COVID-19 transmission in schools and evaluates the impact of weekly screening on controlling school-related infections during the Delta and Omicron waves between 2021 and 2022. The findings reveal that school transmission played a significant role in both periods, accounting for more than 50% of infections. However, the implementation of systematic screening has helped to mitigate silent transmission due to pre-symptomatic and asymptomatic cases. The counterfactual scenario suggests that approximately 40% of school transmissions are prevented by replacing national protocols with weekly screening.

The observed increase in student prevalence during the Delta and Omicron waves compared to the Alpha period (see Chapter 2) suggests an augmented risk of infection in students, likely facilitated by the higher transmissibility of these variants [113, 114], a generally more widespread community circulation of the virus [99] and, lower rates of vaccination and infection-induced immunity in children when compared to adults [93, 99]. We quantified the contribution of school transmission to children infections to disentangle which component among school and community was more prominent during the circulation of those variants and, consequently, understand where to concentrate the efforts. Our results indicate that more than half of the infections in children have occurred within the school setting during the Delta wave and around 50% during the Omicron wave, highlighting the significant contribution of school-based exposure. However, the interplay between within-school and community transmission is not a trivial question since many factors can concur. In high-incidence conditions such as the ones during the Omicron circulation, several separate introductions can penetrate schools. Once transmission is established among students in school, cases can additionally increase and serve as a source to spread infections to household members. A prospective epidemiological investigation of a school outbreak in Geneva during the Omicron period shows that 63% of households experienced infections after their child tested positive [193]. A study in South Korea investigating an outbreak that originated in pediatric facilities similarly reveals that children significantly contributed to onward transmission to their households [194]. This is in line with a retrospective observational study in Germany analyzing the different phases of the pandemic, concluding that contacts in schools were a relevant source of community transmission during the Omicron period when schools were open and testing was mandatory [196].

This study has additional limitations that needed to be acknowledged, beyond those discussed in Section 5.2. Our main analysis considers reduced susceptibility and transmissibility for children. However, recent studies suggest higher values of these epidemiological parameters with the emergence of the Omicron variant [106, 197]. To evaluate the impact of these revised parameters on the results, some sensitivity analysis is necessary. Our preliminary results related to school contributions and the prevention of school infections appear to be robust when assuming that children are as infectious as adults (Figure 5.1). Furthermore, it is important to note that addressing the issue of case detection requires further investigation. A modelling study conducted in the Netherlands, calibrated on multiple source data,

indicates that approximately 50% of cases in the community have been under-reported in children during the Omicron wave [198]. However, this percentage is influenced by the measures implemented and may vary over time, across different countries, and among different departments. To gain a better understanding of this aspect, future analyses can be designed to compare regions with and without weekly screening in place (control case vs. source), thereby estimating the magnitude of under-reporting.

Although other modelling studies simulated reactive screening strategies after a case identification [169, 180], it is worth noting that our study is to our knowledge the first that quantitatively assesses the effectiveness of weekly screening compared to reactive strategies, as well as the contribution of school contacts to transmission during the Delta and Omicron waves from field data.

In conclusion, this study provides a more comprehensive understanding of school transmission, particularly with the emergence of highly transmissible variants such as Delta and Omicron and low vaccination coverage, emphasizing ever more the need for effective policies to control the spread of SARS-CoV-2 within school settings during that phase.

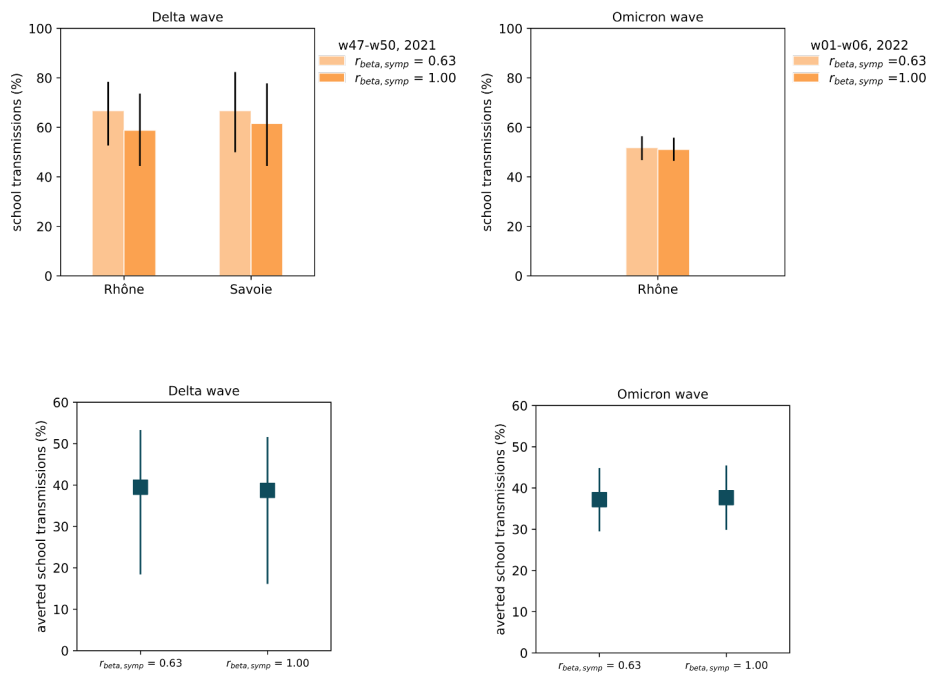


FIGURE 5.1: Percentage of school infections (first row) and averted school transmissions (second row) under weekly screening during the Delta and Omicron waves, assuming children are fully infectious. Black lines represent interquartile range

Conclusions

The COVID-19 pandemic had a significant impact on the lives of children and adolescents, disrupting their daily routines, education, and overall well-being. After the initial shut-down, government focus shifted towards finding ways to keep schools open, recognizing their role in fostering learning and development. The research questions explored in this dissertation were thus conceived to find strategies that could allow for safe in-person learning while enhancing our understanding of COVID-19 school transmission in educational settings.

To achieve these goals, I developed a stochastic agent-based model from primary and secondary school networks of contacts to study the transmission dynamics in various pandemic phases, including the emergence of the Alpha and Omicron BA.1 variants. By fitting the model to field prevalence data collected in France in various periods, I estimated the transmission rate per contact within schools during each phase through a maximum likelihood approach. The estimates provided insights into the school-specific effective reproduction number and the contribution of schools to the total number of infections in children. To identify safe strategies for limiting school discontinuity and transmission while optimizing resources, I simulated a wide range of school protocols. These strategies included testing and isolation of symptomatic individuals, regular and reactive screening of close contacts, and quarantine measures. Most of the simulated strategies followed those applied in France and served to better inform authorities during the management of the COVID-19 crisis [8, 9, 10, 11, 12, 13]. The model also incorporated vaccination to assess its impact to inform recommendations for children of 5-11 y.o. in France [14].

We showed that the transmission of the SARS-CoV-2 virus within schools can be influenced by various factors, including contact patterns among students, the incidence of the virus in the community, the emergence of variants, and the effectiveness of control measures. The estimates of the school-specific effective reproduction number (R_{school}) during the Alpha wave outbreak in France demonstrated that transmission occurred in both primary and secondary schools, in contrast with previous evidence conveying that schools were not a high-risk setting for SARS-CoV-2 transmission [161, 162]. This finding also underlined the need for more stringent measures to control transmission in schools compared to class closure after case identification. Anticipating the circulation of the Delta variant for the winter of 2021, we identified weekly screening with high adherence (larger than

75%) as the best strategy for reducing the number of cases and minimizing student days lost (see Article #1 in Chapter 3). We showed that the strength of regular screening relied on the early identification and isolation of individuals who may spread the virus without displaying symptoms (pre-symptomatic or asymptomatic forms). These results were well aligned with previous modelling studies [199, 200] and were confirmed later by others [169, 180], demonstrating the robustness of the effectiveness of regular screening. The novelty of our study relied on the integration of empirical estimates of participation levels recorded throughout the pilot and experimental weekly campaigns into the model. The higher performance of weekly screening was preserved also when test resources and high-incidence conditions were considered, such as during the Omicron wave in early 2022 (see Article #2 in Chapter 4). In particular, we showed that the strengthened reactive screening applied nationwide in January 2022 in France implied a similar use of test resources when compared to the weekly screening approach adopted in the Basel canton, Switzerland. However, an unforeseen surge in test demand is caused by the strengthened reactive screening with very limited control compared to the weekly screening. This lack of predictability in the reactive screening approach had cascading effects on schools and families, which were undermined by continuous requests for testing and discontinuities in school activities. Through scenarios, I also evaluated the impact of vaccination, revealing that it could provide significant collective protection in the short term if vaccination coverage was extensive. Instead, when coverage was low or moderate, regular screening remained an important strategy to detect a substantial number of infections that would have gone unnoticed, if reactive class closure or reactive screening were in place. Through a real-world experiment, I found that during the more transmissible Delta and Omicron variants, transmission episodes within schools accounted for about half of the cases or more. In addition, by comparing the outcomes of the experimental screening and the national strategy, I could confirm the previous modelling evidence of the effectiveness of weekly screening in preventing school transmission with respect to reactive screening (see Article #3 in Chapter 5).

Overall, in this thesis, I provided some clear conclusions on the mechanism underlying school transmission, the role of asymptomatic infections, and the school contribution to total infections. Contact measurements with RFID sensors from a pre-pandemic period were one of the strengths of this work, since they allowed us to capture contacts with a high temporal resolution and to develop an agent-based approach that makes an explicit notion of the individual. This was particularly important for intervention modelling purposes, especially when interventions were triggered at the individual level or targeted at specific classes (reactive closure or screening) or contacts (cohorting). Moreover, the use of empirical networks allowed us to reduce the number of parameters to those strictly related to the epidemiological component. Most of them, such as the time spent in each compartment, were taken from literature, while the transmission rate was fitted to reproduce observations. However, in the absence of detailed temporal contact data, information extracted from surveys and synthesized in a contact matrix could represent a valid alternative. This solution is especially advantageous to study the spread at the population level and across age classes, when detailed contact data collection may become expensive. In this case, the resulting model would

have the form of an age-stratified compartmental model. Examples are those used to assess the impact of school reopening on COVID-19 [201] or influenza circulation [36].

The work presented in this thesis also has some limitations, as highlighted in the past Chapters. Although the model was mostly empirically data-driven, some level of uncertainty was still associated with the underreporting factor in the notified cases. In the analysis, we first informed these values from the literature. However, this value might have changed over time because of a different attitude towards testing and the broader availability of tests. At the start, it was plausible that children could be more affected by underreporting because they were more prone to be asymptomatic and therefore not detected. However, the advent of self-testing, largely used during the Delta and Omicron waves [150], in addition to reactive screening strategies in schools, may have lowered this underreporting in France. Transmission events were modelled upon contact only with an infectious individual and no other routes were considered. In other contexts, it would be beneficial to include also this route and assess its contribution. Finally, our analysis of field data was limited to a relatively short time interval (2 weeks during the pilot screening in Spring 2021, and 6 weeks in the 2 rounds of experimental screening in winter 2021-2022) while longer periods of application would have allowed a more complete representation of the changes in school contribution and relative protocols effectiveness over time.

Based on these elements, some natural extensions are possible. In Basel Canton, Switzerland, weekly screening was implemented from March 2021 to February 2023 [182]. We have access to the student prevalence data for part of this period. Therefore, we could now use our approach to investigate COVID-19 transmission over extended timeframes and for different variants and contexts. To better characterize contacts in another country, we could construct temporal networks from data on average school and class sizes. Additionally, since other cantons employed different strategies during the same period, this would represent a natural opportunity for a case-control comparison, allowing us to assess the effectiveness of one protocol versus the other in practical conditions.

During the COVID-19 pandemic, the circulation of respiratory diseases, including influenza and the respiratory syncytial virus (RSV), declined in many countries [202, 203, 204]. In the season of 2022-2023, influenza virus activity returned to almost pre-pandemic levels in the European countries, with an earlier start and higher positivity peaks compared to the four previous seasons [205]. Notably, out-of-season activity was recorded in August 2022 in the Cycladic Islands, Greece [206]. Similarly, RSV saw increased transmission rates and an earlier-than-usual season start [207]. Recently, Australia experienced an early influenza season in June 2023, with children being particularly affected compared to other age groups [208]. The decline in influenza and RSV cases observed during the initial stages of the COVID-19 pandemic can be largely attributed to the strict public health measures implemented, including mandatory mask-wearing, physical distancing, curfews, and restrictions on gatherings. These measures not only effectively reduced COVID-19 cases but also had a positive impact on controlling the transmission of other respiratory diseases, such as influenza and RSV [204, 209]. On the other hand, this decline in the circulation of influenza

and RSV during the pandemic also led to a sort of ‘immunity debt’ [209]. The reduced exposure to these viruses resulted in a lack of natural immunity, creating a large reservoir of susceptible individuals when strict measures were eased. Consequently, altered seasonal patterns and a marked increase in cases of influenza and RSV were observed. In winter, we expect a co-circulation of SARS-CoV-2, influenza, RSV, and other respiratory viruses, particularly affecting children. This situation may be more challenging if vaccines for certain viruses, like RSV, are not yet officially available, or if vaccination coverage in children remains low or decreases over time, as seen with COVID-19 [178].

In this context, understanding the transmission dynamics of these viruses in schools remains important. Schools represent densely populated settings where respiratory droplets and aerosol dispersion can be dominant modes of transmission in the absence of preventive and control measures. In this last case, small particles containing the virus can indeed remain suspended in the air and be inhaled by other students in the same room, representing an additional transmission route besides proximity contacts. Thus, investigating how influenza, RSV, or both could spread in such environments would allow us to assess the burden of respiratory viruses in children, identify patterns, and design effective mitigation strategies. The agent-based model I have developed is well-suited for characterizing transmission in school settings. It can thus be adapted to study the transmission of influenza, RSV, or both in the years following the COVID-19 pandemic.

In perspective, it would be interesting to integrate into the model environmental data on aerosol concentration in classes, as collected in Italy, in the Marche region, and in Switzerland in the context of COVID-19 [210, 211]. In such a way, we could characterize the contribution deriving from each possible transmission route. Secondly, determining the interplay between direct and indirect transmission of a respiratory virus would have the potential to help identifying the most effective school-based interventions. The mode of transmission (proximity-based or airborne) may vary among different respiratory viruses and be influenced by their distinct clinical characteristics, such as susceptibility, transmissibility, and the presence of asymptomatic cases. A comprehensive understanding of these aspects would better inform decision-making processes and simplify the selection of the most effective intervention strategies.

Currently, the primary recommendations for preventing and controlling the transmission of respiratory viruses include staying home when ill, practising good hand hygiene, following respiratory etiquette, keeping physical distancing, and wearing a face mask [212, 213]. In the near future, it would be beneficial to study the impact of ventilation on reducing particle concentration and its relation to transmission rates during different seasons. Understanding the frequency and type of ventilation that produces a lower transmission can inform the design of more effective ventilation strategies. Ventilation measures offer an additional advantage as they are non-invasive compared to physical distancing and face mask requirements, which were necessary during the pandemic. Compliance with physical distancing and mask-wearing, especially among children, can be hard to follow, as indicated by a longitudinal study on COVID-19 prevention measures in English schools [214]. The

study also highlighted the importance of social interactions for children educational experiences, suggesting that interventions should consider behavioral factors and the feasibility of compliance.

In the years following the COVID-19 pandemic, we should minimize interventions that can highly impact children and promote all those actions that favour the regular school life. According to the WHO bulletin, 138 school closure days occurred on average between January 2020 and December 2022 in the 22 countries and regions studied (maximum: 341 missed days in Italy) [215]. The inadequate access to in-person education caused by the pandemic is estimated to have produced a loss of 17 trillion in lifetime earnings [216]. To invert this trend, in-person learning should be maximized in the next few years. Mathematical models, such as the one proposed in this thesis, provide a valuable tool to assess the effectiveness of various interventions through simulations, considering specific conditions and outcomes. In particular, it would enable to synthetically test the potential impact of different measures, either alone or in combination, to develop evidence-based strategies for the management of respiratory virus transmission.

In the past, participatory surveillance systems, such as *Influenza.net*, were designed to conduct syndromic surveillance by relying on self-reported symptoms [217] in order to develop warning systems through the monitoring of potential changes. With the advent of COVID-19, surveillance systems were significantly strengthened. However, distinguishing symptoms between positive SARS-CoV-2 cases and other respiratory pathogens can be challenging in children [218]. An alternative approach to enhance the assessment of respiratory virus burden in school-aged children could be through multi-virus testing and continuous surveillance. By providing diagnostic kits in schools, early identification of symptomatic children would be facilitated, and protection for children with underlying risk factors would be prevented.

Outside the European context, the CDC recommends the implementation of COVID-19 screening for both unvaccinated and vaccinated students in strategic periods of the year to support safe in-person learning [219]. These key moments may include before or after significant events, such as returning from breaks (e.g., holidays or the beginning of the school year), during school outbreaks, or periods of high hospital admissions. These screening measures can be effectively discontinued when the period of high community transmission ends. This approach could be potentially extended to manage other respiratory viruses, if governments have enough resources.

To enhance the accuracy and robustness of public health models, various data streams can be integrated. Gathering behavioural data on contacts, ranging from fine to raw resolution, is essential to understanding transmission patterns. This information can help identifying high-risk behaviours and develop targeted interventions based on contacts to curb disease transmission effectively. Moreover, qualitative surveys investigating the response to specific measures would allow us to understand the acceptability. Moreover, conducting seroprevalence studies can be important in determining the proportion of the population that has been exposed to the virus and developed antibodies. Combining these data with

other surveillance information can significantly improve modelling efforts, reducing the reliance on assumptions and associated limitations.

In conclusion, even if children typically experience less severe COVID-19 disease compared to adults (which is different from what is typically seen with other respiratory viruses such as RSV [220]), we demonstrated with this thesis that school contacts can represent an important source of infections. We explored ways to guarantee safe school access during the different phases of the COVID-19 pandemic. The findings of this dissertation were used over the course of the pandemic to guide public authorities in their decision-making processes. The modelling framework can be extended to include other respiratory pathogens, and it can still be valuable in informing policy and decision-making for the design and implementation of future strategies against respiratory viruses.

Inference framework

A.1 Maximum likelihood estimates

Pilot campaign on March 2021, France

Figure A.1 shows the maximum likelihood estimates for the transmission rate β . The parameter β was estimated with maximum likelihood using a grid-based exploration with 5000 simulations for each value. The MLE corresponds to the transmission rate per contact estimated for the Alpha variant as this variant accounted for >90% of all positive tests in the study period.

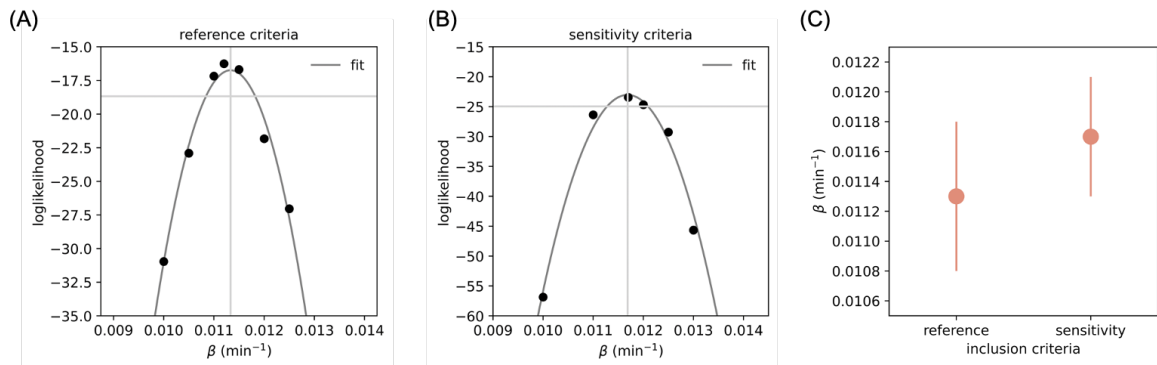


FIGURE A.1: (A) Loglikelihood for the reference inclusion criteria, the vertical line corresponds to the estimate, and the horizontal line represents the 95% confidence interval obtained using likelihood ratio. (B) As in (A) for the sensitivity inclusion criteria. (C) MLEs for the reference and sensitivity inclusion criteria. The error bars correspond to the 95% confidence intervals.

Figure A.2 shows the predictions of the model for the school prevalence obtained with the maximum likelihood estimate of the transmissibility per contact compared to the observed prevalence at school obtained from the pilot screening data.

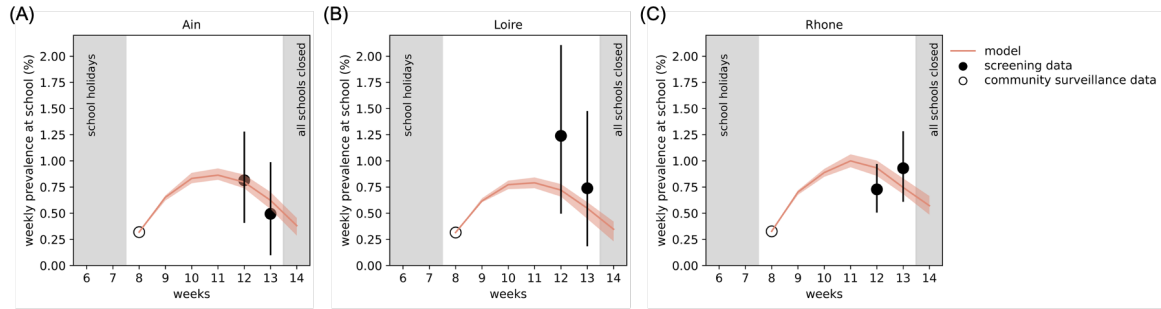


FIGURE A.2: Prevalence at school (model vs predictions) during the 2021 spring wave. From left to right: Ain, Loire, Rhône department. Model predictions for the school prevalence are obtained with the maximum likelihood estimate of the transmissibility β per contact. White dots represent the inferred prevalence at school obtained from community surveillance data; black dots represent the observed prevalence at school obtained from screening data. Error bars correspond to 95% confidence intervals.

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