

Evidence of Transmission and Circulation of Deltacron XD Recombinant Severe Acute Respiratory Syndrome Coronavirus 2 in Northwest France

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In February 2022, samples collected in northwest France showed discordant molecular results. After virological and epidemiological investigations, 17 cases of Deltacron XD recombinant severe acute respiratory syndrome coronavirus 2 were confirmed by sequencing or suspected due to epidemiological links, showing evidence of an extended transmission event and circulation of this form, with low clinical severity.

Keywords. Deltacron; chain of transmission; recombination; SARS-CoV-2; variants.

The Coronaviridae family is composed of positive-sense, single-stranded RNA viruses, characterized by high plasticity and genetic diversity. Frequent genetic recombination events are described in this group, including in human coronaviruses (hCoVs). Although the mechanism remains unclear, the generation of a set of subgenomic RNAs contributes to promote homologous recombination events [1]. Given the behavior of other hCoVs, recombination between variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was considered likely, especially in a context of massive co-circulation of variants in the same geographic area where the likelihood of

coinfection is high [2, 3]. These events could lead to the emergence of a transmissible recombinant form, with an unknown fitness, unpredictable potential (in particular considering a new pandemic wave), and possible resistance to current treatments or vaccines combining those of progenitors.

SARS-CoV-2 variants are grouped according to their lineage (phylogenetic distribution) [4] and clade (component mutations) [5]. In January 2022, variants of concern 21A/I/J Delta (B.1.617.2/AY.*) and 21K/L/M Omicron (B.1.1.529/BA.*) were predominant, with a high level of co-circulation in most of the world, including France. At the end of January, Delta + Omicron dual infection cases were documented in France [6, 7]. Delta-Omicron recombinants, with an Omicron-like spike in the Delta genome backbone, were reported in Denmark and the Netherlands at the beginning of February [8]. The co-circulation of different lineages may promote recombination and multiple recombination patterns could potentially emerge as already observed in other hCoVs such as hCoV-OC43 [3, 9]. Genomic and epidemiological analyses are therefore essential to differentiate transmission of a given recombinant from simultaneous independent emergences.

On 3 February 2022, samples collected at Rouen University Hospital from a man (DOREC345) and his daughter-in-law (DOREC248), sharing the same household, showed discordant molecular results, between an in-house variant screening test and full-genome next-generation sequencing ([Supplementary Materials](#)). These results led to a more in-depth investigation of the sequencing data. Phylogenetic and recombination analysis highlighted Omicron signature mutations in the spike region and Delta signature mutations in the rest of the genome ([Supplementary Materials](#)). Recombination detection algorithms suggested a Delta-Omicron recombinant form, now known as Deltacron XD, with 2 breakpoints: the first one, with a Delta-Omicron pattern at the beginning of the spike region (22034–22194) and the second, with an Omicron-Delta pattern, at the beginning of ORF3a (25469–25584) ([Figure 1](#), [Supplementary Figure](#), [Supplementary Materials](#)).

Three additional coding mutations described as signature mutations of this Deltacron XD recombinant form were observed: ORF1a:I2820V, S:A27S, and S:N764K. On the detected recombinant region, the spike of Deltacron XD was identical to the spike of Omicron, with the notable exception of the N764K mutation which, at this scale, impacts notably the identity calculation. The search for Delta and/or Omicron parental strains (ie, coinfection) was negative, confirming transmitted recombinant forms.

When these discrepancies were observed, Santé publique France (the French national public health agency) was tasked

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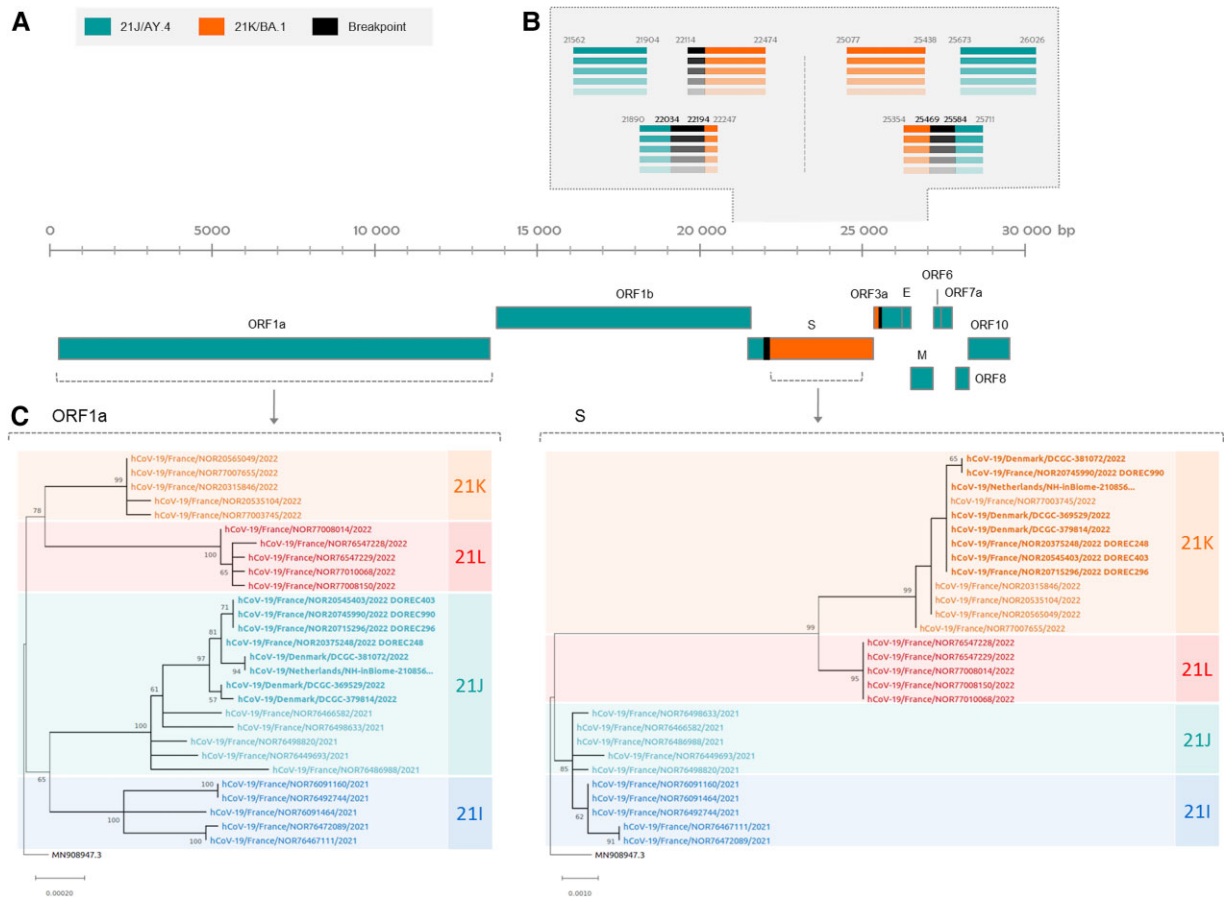


Figure 1. A, Pattern of Deltacron XD recombinant forms. B, Visualization of reads obtained around the breakpoints. Amplicon and breakpoint locations are indicated relative to the numbering in the Wuhan-Hu-1 reference strain (GenBank accession number MN908947) [10]. C, Phylogenetic analysis of the complete open reading frame (ORF) 1a and S regions of 28 severe acute respiratory syndrome coronavirus 2 strains. The phylogenetic trees were constructed using maximum composite likelihood approach. Bootstrap values were calculated from 500 replicates. Only bootstrap values >50% are shown [11]. The evolutionary distances were computed using the general time-reversible model. A discrete Gamma distribution was used to model evolutionary rate differences among sites (5 categories with parameter = 0.1000). The rate variation model allowed for some sites to be evolutionarily invariable. Evolutionary analyses were conducted in MEGA X [12]. Confirmed cases of recombinants are written in bold and the case code is indicated in square brackets. The confirmed DOREC345 case does not appear on the phylogenetic trees, owing to a low sequencing coverage.

to conduct epidemiological investigations, while the National Reference Center for Respiratory Viruses (Institut Pasteur) proceeded to molecular and pattern confirmation.

Epidemiological investigations were conducted by phone between 2 February and 3 March 2022, using a standardized questionnaire to obtain information on demographics, travel history, clinical symptoms and outcomes, risk factors, previous SARS-CoV-2 infection, and vaccination status. A suspected case was a person positive for SARS-CoV-2, diagnosed by reverse-transcription polymerase chain reaction (RT-PCR), antigen test, or rapid antigen self-test, and who had been in close contact (ie, prolonged contact within 2 m) with a confirmed case. A probable case was a person with a BA.2–like variant screening test and who had been in close contact with a confirmed case. A confirmed case was a person with whole genome

sequencing results identifying the Deltacron XD recombinant. The activities of all cases were mapped to establish potential exposures and identify transmission chains (Figure 2). Contact tracing was carried out to determine the source of exposure and exposed individuals.

The first 3 cases identified, including 2 confirmed cases (DOREC248 and DOREC345, diagnosed on 23 January and 27 January 2022, respectively) and 1 probable case (DOREC141 diagnosed on 24 January 2022), lived in the same household (Figure 2). Four additional suspected cases related to this household were also reported: 2 other children of the family and their grandparents. DOREC248 was a child who attended nursery school and who shared an epidemiological as well as a phylogenetic link with DOREC403 (confirmed case, diagnosed on 3 February 2022). Indeed, 1 child of

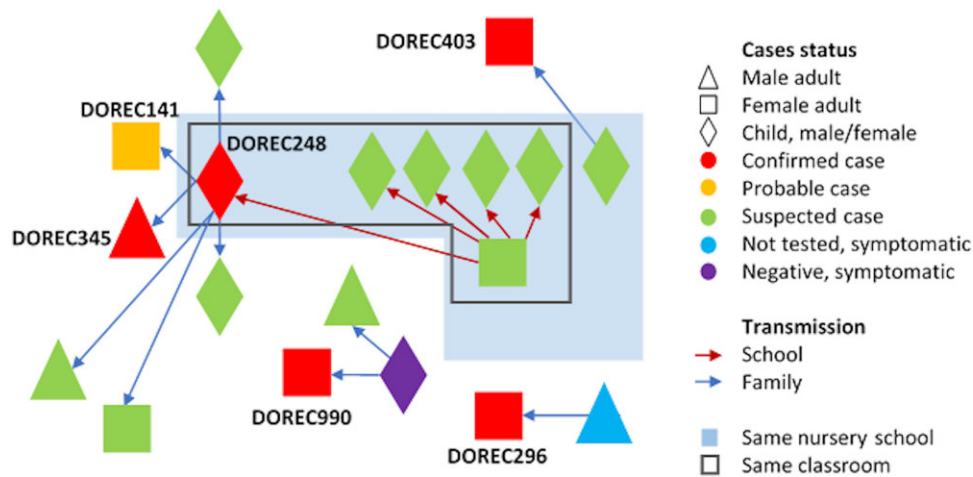


Figure 2. Probable transmission chains of reported cases of Deltacron XD recombinant severe acute respiratory syndrome coronavirus 2 occurring between January and February 2022. In this investigation, a confirmed case was a person with whole genome sequencing results identifying the Deltacron XD recombinant. A probable case was a person with a BA.2–like variant screening test and who had been in close contact (ie, prolonged contact within 2 m) with a confirmed case. A suspected case was a person positive for coronavirus disease 2019, diagnosed by reverse-transcription polymerase chain reaction, antigen test, or rapid antigen self-test, and who had been in close contact with a confirmed case.

DOREC403 was positive a week before her and attended the same nursery school as DOREC248; he was therefore considered as a suspected case. The investigation of this nursery school identified 5 more suspected cases: 4 children and 1 adult, who were positive between 19 and 26 January. This adult, diagnosed on 19 January 2022 was the first of all investigated cases. Two additional confirmed cases (DOREC296 and DOREC990, diagnosed on 14 February and 17 February 2022, respectively) were identified but did not show a clear epidemiological link with the other confirmed cases. DOREC296 stated that her husband had infected her; the latter, although not tested, had exhibited symptoms including fever and anosmia a few days before her. DOREC990 was positive using RT-PCR as part of her hospital admission (non–coronavirus disease 2019 [COVID-19] related), but she already had a positive antigen test on 6 February 2022. She suggested that her symptomatic but negative daughter, in whose nursery school several cases had been reported, was the source of her infection. These cases were linked to another additional suspected case, her husband, who was positive on 9 February 2022.

Thus, a total of 5 confirmed, 1 probable, and 11 suspected cases of Deltacron XD recombinant SARS-CoV-2 were identified between 19 January and 17 February 2022 (Figure 2). The correspondance between the Deltacron XD recombinant code and the GISAID accession number and the sampling date of each confirmed case are presented in Supplementary Table 1.

The clinical data of all cases (n = 17) are described in Supplementary Table 2. Eight cases were ≤12 years of age and the median age was 35 years (min–max, 5–67 years). Only 2 cases (2 children) were asymptomatic. All others

reported symptoms, the most common being fever (n = 9), runny nose (n = 8), sore throat (n = 8), and fatigue (n = 8). DOREC990 experienced mild ageusia. The median duration of symptoms was 3.5 days (min–max, 1–20 days). DOREC403 still had symptoms of generalized fatigue, shortness of breath, and heart palpitations 20 days after symptom onset. A 62-year-old male patient was treated for hypertension. One confirmed case reported a previous SARS-CoV-2 infection in October 2020. Nine of 10 eligible cases were vaccinated, including a booster dose for those who were eligible.

In-depth virological and epidemiological investigations have proven the transmissibility of the Deltacron XD recombinant form of SARS-CoV-2, in an intrafamilial context and related to at least 1 transmission cluster in school. The detection of sporadic cases with no epidemiological link, but sharing the same genetic pattern and which are very closely phylogenetically linked, has highlighted the circulation of this recombinant since 19 January 2022 in 1 area of Normandy. As observed in the phylogenetic trees, our sequences were closely linked to those found in Denmark and the Netherlands, suggesting that this recombinant had already been circulating at very low levels for several weeks. The hypothesis of a simultaneous emergence of the same pattern cannot be excluded, but seems less likely as breakpoint distribution along the viral genome appears to be random in coronavirus recombinant forms [9]. These points will need to be addressed.

The rapid replacement of the Delta variant by the Omicron variant on a global scale has illustrated the increased transmissibility of Omicron compared to previous variants, including the Delta variant [13]. Data from phenotypic studies of variants

that preceded Omicron indicate that increased transmissibility may be associated with several factors, as well as a major role of the spike protein (especially high affinity for the ACE2 receptor and immune escape) [14]. Like the spike of this recombinant form derived from Omicron BA.1, it should present the same properties, but the impact of Delta AY.4 fragments in the genome remain to be explored, in particular regarding potentially increased virulence.

Many analyses have shown a mild clinical picture and the absence of serious forms linked to the Omicron variant [15]. Case data suggest low clinical severity, but it is very difficult to conclude owing to the median age, the vaccination status, and the small number of cases. Thus, it is not possible to predict the characteristics of such a recombinant compared to its parental forms and to anticipate its impact on public health. The successful isolation of this recombinant (presenting an identical sequence compared to the original clinical sample, data not shown), will allow the study of virological properties, as well as susceptibility to current treatment.

In conclusion, this work has shown evidence of an extended transmission event and the circulation of the Deltacron XD recombinant virus in one area of Normandy, France, which requires close surveillance and monitoring. Multiple questions concerning its origin, virulence, resistance, and evolution remain to be addressed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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