PROPOSED TITLE: "Comparing the evolutionary dynamics of predominant SARS-CoV-2 virus lineages co-circulating in Mexico"

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ABSTRACT (150/150 WORDS)

Up to November 2021, over 200 different SARS-CoV-2 lineages circulated in Mexico. To investigate lineage replacement dynamics, we applied a phylodynamic approach to explore the evolutionary trajectories of five dominant lineages that circulated during the first year of the local epidemic. For most lineages, peaks in sampling frequencies coincided with different epidemiological waves of infection in the country. Lineages B.1.1.222 and B.1.1.519 showed comparable dynamics, represented by clades likely originating in Mexico and persisting for over a year. Lineages B.1.1.7, P.1 and B.1.617.2 also displayed similar dynamics, characterized by multiple introduction events leading to a few successful extended local transmission chains that persisted for several months. We further explored viral movements across the country, applied within the largest clades identified (belonging to lineage B.1.617.2). Many clades were located within the south region of the country, suggesting that this area played a key role in the spread of SARS-CoV-2 in Mexico.

MAIN TEXT (7179/5000 WORDS)

INTRODUCTION

Genome sequencing efforts for the surveillance of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has granted public access to a massive number of virus genomes generated worldwide (https://www.gisaid.org/). Exploring SARS-CoV-2 genome data using molecular evolution tools has enabled to characterize an increasing virus diversity [1], to track emerging viral subpopulations, and to explore virus evolution in real-time both at local and global scales (for examples see [2–6]). Throughout the development of the COVID-19 pandemic, viral variants have emerged and circulated across different regions of the world [2,7], displaying specific mutations that define their phylogenetic clustering patterns [8,9]. SARS-CoV-2 virus lineages have been classified using a dynamic nomenclature system ('Pango system', Phylogenetic Assignment of Named Global Outbreak Lineages), developed to consistently assign newly generated virus genomes to existing lineages, and to designate novel virus lineages according to their phylogenetic identity and epidemiological relevance [10,11].

The emergence and spread of SARS-CoV-2 virus lineages has been routinely monitored since early 2021 (https://www.gisaid.org/), prompted by public health authorities to inform on the ongoing responses to the pandemic [12]. Virus lineages that may pose an increased risk to global health are classified as Variants of Interest (VOIs), Variants under Monitoring (VUMs), and Variants of Concern (VOC), and may display some of the following biological properties [9,13] : increased transmissibility [14], decreasing the effectiveness of available diagnostics or therapeutic agents (such as monoclonal antibodies)[15], and evasion of immune responses (including vaccine-derived immunity) [12,16,17]. Up to date, five distinct SARS-CoV-2 lineages (including their descending sub-lineages) have been designated as VOC: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and more recently, the B.1.1.529 lineage (Omicron) [12,18,19].

The spread of variants in different regions of the world has been linked to human movement, with VOC often replacing previously circulating virus lineages to become dominant (for example, see [20]). Virus lineages that dominate across distinct geographic regions are likely to denote an evolutionary advantage, driven in part by a genetic background prompting some increase in fitness (such as enhanced transmissibility and/or immune escape) [20–24]. However, whilst some lineages may become dominant in some geographic regions, others fail to do so [20]. Exploring lineage replacement

dynamics remains challenging, as it represents a complex scenario impacted by numerous factors, such as: i) differential and stochastic growth rates linked to lineage-specific spread patterns varying across geographic regions, ii) a genetic background and a shifting immune structure of the host population (linked to viral pre-exposure levels, as well as vaccination rates),[20,24] and iii) changing behavioural patterns, such as fluctuating human mobility and the implementation of local non-pharmaceutical interventions across time [20,25,26].

Mexico has been severely impacted by the COVID-19 pandemic, evidenced by the high number of cumulative deaths reported relative to other countries in Latin America [27]. Since the first introductions of the virus into the country during early 2020 [28], the development of the local epidemic has been characterized by an epidemiological curve fluctuating between three waves of infection observed in July 2020, January 2021, and August 2021 (up to November 2021) [27–29]. Prior to the peak of the first wave, non-pharmaceutical interventions including social distancing and suspension of non-essential activities were implemented at a national scale (from March 23rd 2020 to May 30th 2020), whilst a reopening plan for the country was announced on May 13th 2020. Further, the national vaccination campaign did not began until December 24th 2020 [27].

During February 2021, a sequencing consortium for the surveillance of SARS-CoV-2 in Mexico was launched (Mexican Consortium for Genomic Surveillance, abbreviated CoViGen-Mex [30]). In an attempt to further homogenize the spatial and temporal representation of the viral genomes sequenced, the sampling scheme was upgraded in May 2021, for which approximately 1,200 representative samples selected across all states following official case reports were sequenced monthly [30]. This resulted in approximately one third of the virus genome sequences from Mexico publicly available. Independent to CoViGen-Mex, other national institutions significantly contributed to the genomic surveillance of the virus (https://www.gisaid.org/). Sequencing efforts at a local scale have enabled to characterize viral diversity, and to identify the viral lineages circulating within national territory [30–32]. Over 200 different virus lineages have been detected in Mexico, including all VOC [19,33]. Many lineages also co-circulated across time and space, an observation of particular importance in the context of the recently described recombinant SARS-CoV-2 linages that emerged in North America during 2021 [34].

Using a phylodynamic approach, we used publicly available virus genome data collected in Mexico to investigate the introduction, spread and replacement patterns of predominant virus lineages

(B.1.1.222, B.1.1.519, B.1.1.7, P.1 and B.1.617.2) that circulate(d) in the country up to November 2021. To generate datasets, we implemented a migration and a phylogenetically-informed subsampling approach, aiming to increase robustness for tailored phylogeographic analyses. We further explored the correlation between human mobility and the inferred viral movements for the largest clades (C5d and C6d) belonging to the B.1.617.2 lineage, which also represented the most extended transmission chains. Analysis revealed similar dynamics for the B.1.1.222 and B.1.1.519, with both of these likely originating in Mexico and showing a sustained transmission over a year. For the P.1, B.1.1.7 and the B.1.617.2, multiple introduction events were identified, with few large transmission chains representing successful viral spread across the country. For C5d, spread occurred from the south, with subsequent movement into the central and northern region of the country. Our study further provides the basis for in-depth exploration of SARS-CoV-2 genomic data from Mexico, and highlights the need to investigate the spread of transmission chains at a state level resolution.

RESULTS

Prior to the introduction of 'Omicron' (B.1.1.529) into Mexico, only the B.1.1.222, B.1.1.519, B.1.1.7 (Alpha), P.1 (Gamma) and B.1.617.2 (Delta) virus lineages showed a progressive replacement pattern to become dominant over other co-circulating virus lineages, with peaks in sampling frequency often coinciding with the epidemiological waves of infection (except for B.1.1.7 and the P.1; **Figure 1a and b**) [19,31,32]. During this time, Mexico reported a daily mean test rate ranging between 0.13-0.18 test/1,000 inhabitants, approximately 19 times lower than the global daily median test rate recorded at the time [29]. Despite testing limitations, the number of viral genomes generated at a national scale correlates with the cumulative number of cases recorded throughout the development of the epidemic (up to March 2022), with the majority of genomes coming from Mexico City (**Supplementary Figure 1**). In average, 100 genomes per 10,000 cases have been generated, corresponding to approximately 1% of the official COVID-19 cases reported. The distribution of genomes sequenced across states apparently coincides with the reported numbers of active and cumulative confirmed cases at the time [35,36,37]. Nonetheless, this is likely impacted by an uneven genome sequencing across states (particularly evident during the first year of the epidemic), and by differences in the sequencing intensity across time.

- B.1.1.222

The B.1.1.222 lineage circulated between April 2020 and September 2021, mostly sampled from the USA (77% of all sampled sequences) and Mexico (22% of all sequences), with a limited detection in other regions of the world (as reported in https://cov-lineages.org/) [38]. However, the apparent proportion of genome sequences sampled from different countries reflects sequencing biases across locations. The first B.1.1.222-assigned genome was collected from Mexico on the 04/04/2020 (Mexico/CMX-INER-0026/2020-04-04) [38], whilst the last B.1.1.222-assigned genome was collected from the USA on the 14/09/2021 (USA/CA-CDPH-1002006730/2021-09-14). The last B.1.1.222-assigned genome from Mexico dates to the 26/07/2021 (Mexico/CHH_INER_IMSS_1674/2021-07-26), two months before the latest collection date for the B.1.1.222 lineage at an international scale.

The B.1.1.222 lineage was continuously sampled from the country between April 2020 and May 2021, followed by a steady decline in detection after July 2021 (**Figure 1b**). Most of the genome sampling corresponds to the central region of the country, represented by Mexico City (CMX; **Figure 2a**). Data corresponding to the first year of the epidemic showed that by February 2021, the B.1.1.222 had reached a cumulative frequency of approximately 10% relative to other virus lineages co-circulating within national territory [32]. Our results show that the sampling frequency of the B.1.1.222 in Mexico progressively increased after June 2020, initially coinciding with the peak of the first epidemiological wave in the country, further reached a highest of up to 35% in October 2020 **(Figure 1b)**. Thus, the B.1.1.222 lineage is likely associated with the observed increase in the number of cases at that time. An initial frequency underestimation for the B.1.1.222 lineage is attributable to a limited and centralized virus genome sequencing during the first year of the epidemic in the country.

Phylogenetic analysis revealed a main clade deriving from a single MRCA (most recent common ancestor; here denoting lineage emergence), with subsequent introductions into other countries (namely the USA; **Figure 2a**). The inferred date for this earliest MRCA corresponds to March 2020, a month before the earliest collection date of the first B.1.1.222-assigned genome (Mexico/CMX-INER-0026/2020-04-04; **Figure 2a**). During this time, the B.1.1.222 was likely to be seeded into the USA from Mexico multiple times; thus, all subsequent inferred introduction events are interpreted as ‘re-introductions’. In this context, our analysis revealed a minimum of 237 distinct introduction events from Mexico into the USA (95% HPD interval = [225-250]), and a minimum of 106

distinct events from the USA into Mexico (95% HPD interval = [95-122]; **Figure 2a**). The dates inferred for re-introduction events ranged from October 2020 to July 2021. The B.1.1.222 lineage displayed a total persistence of up to 16 months.

- B.1.1.519

Descending from the B.1.1.222, the B.1.1.519 lineage was first detected in North America, being mostly sampled in the USA (58% of all sequences) and Mexico (32% of all sequences, as reported in https://cov-lineages.org/) [32,39–41]. Again, the proportion of genomes from different countries reflect sequencing biases across geographic regions. The first B.1.1.519-assigned genome was collected in the USA on the 31/07/2020 (USA/TX-HMH-MCoV-45579/2020-07-31) [42], with the lineage being last detected on December 2021 [43]. During our initial phylogenetic assessment, most of the B.1.1.519-assigned genomes collected after November 2021 were identified as outliers, and were excluded from further analyses. Of note, these genomes were sampled from countries where the lineage was not reported to be locally circulating (namely Turkey and Africa).

In Mexico, the B.1.1.519 lineage was first detected on the 28/08/2020 (Mexico/YUC-NYGC-39037-20/2020-08-28) and was last detected on the 01/11/2021 (Mexico/CAM_IBT_IMSS_4057/2021-11-01) [32]. By late February 2021, the B.1.1.519 represented the majority of the viral genomes from the country [32,41]. The spread of the B.1.1.519 lineage raised awareness in public health authorities, [32,40,41], leading to its designation as a VUM in June 2021 [12]. Cumulative virus genome data shows that by January 2021, the B.1.1.519 progressively displaced other co-circulating virus lineages, representing up to 75% of all virus genomes generated from the country, and dominating during the peak of the second wave of infection (**Figure 1a and b**). Most of the genome sampling again corresponds to the central region of the country, represented by the state of Puebla (PUE; **Figure 2b**).

Phylogenetic analysis revealed a pattern similar to the one observed for the B.1.1.222, with an earliest MRCA leading to a single clade from which subsequent dispersal events into other countries occurred (namely USA; **Figure 2b**). This earliest MRCA dates to July 2020, again representing lineage emergence within the country. Our analysis suggests that the B.1.1.519 circulated cryptically in Mexico for four months prior to its initial detection, being seeded back and forth between the USA and Mexico during this time (**Figure 2b**). Such observations are congruent

with the collection date of the earliest B.1.1.519 genome sampled globally (July 2020, USA/TX-HMH-MCoV-45579/2020-07-31), positioned basally to the B.1.1.519 clade. As only good-quality sequences were included within our dataset, two earlier genome sequences from Mexico excluded from our datasets collected between August and October 2020 (Mexico/YUC-NYGC-39037-20/2020-08-28 and Mexico/CMX-INER-IBT-0485/2020-10-13) suggest that the cryptic circulation period for the lineage could have been shorter. We estimated a minimum number of 121 introduction events from the USA into Mexico (95% HPD interval = [109-132]), compared to a minimum number of 391 introduction events from Mexico into the USA (95% HPD interval = [380-402]), all occurring between July 2020 and November 2021 (the latter represented by sequence Mexico/CAM_IBT_IMSS_4057/2021-11-01; **Figure 2b**). The B.1.1.519 lineage displayed a total persistence of approximately 16 months (earliest collection date: 28/08/2020, latest collection date: 01/11/2021).

- B.1.1.7

The B.1.1.7 lineage was first detected in the UK during September 2020, spreading to over 175 countries in over a year [44]. The earliest B.1.1.7-assigned genome from Mexico was first collected on the 31/12/2020 (Mexico/TAM-InDRE-94/2020-12-31), and the latest on the 13/10/2021 (Mexico/QUE_InDRE_FB47996_S8900/2021-10-13). Cumulative data showed a continuous lineage detection for over ten months, with a sampling peak observed around May 2021, followed by a steady decline with almost no detection by late August 2021 (**Figure 1b**). Relative to the epidemic in the country, the circulation of the B1.1.7 in Mexico coincided with a lower number of recorded cases observed during May-June 2021 [27,29,45]. Overall, the B.1.1.7 lineage reached a lower genome sampling frequency (of up to 25%), compared to the other virus lineages studied here (**Figure 1b**). Most of the genome sampling corresponds to the northern region of the country, represented by the state of Chihuahua (CHH; **Figure 3a**).

Phylogenetic analysis revealed a minimum of 224 introduction events into Mexico (95% HPD interval = [219-231]; **Figure 3a**), with an earliest MRCA dating to October 2020, denoting a cryptic circulation period of approximately two months. Subsequent introduction events occurred between March and June 2021, with a total lineage persistence of ten months. Seven clades (C1a to C7a) were identified to represent large local transmission chains (composed of >20 sequences from Mexico with ancestral nodes supported by a PP value >.80; **Figure 3a, Supplementary Data 2**). The earliest

genome sequences were collected from the north-east region of the country (mostly represented by the state of Chihuahua, CHH) [32,46] and fall within the C2a identified here, with an MRCA dating to late January 2021 (**Supplementary Data 2**). Of note, the collection date of the earliest B.1.1.7 genome from Mexico coincides with at least four independent introduction events that occurred synchronously during December 2020 (**Figure 3a**).

The C3a and C7a were identified as the largest clades, with both MRCAs dating to February 2021, denoting again independent and synchronous introduction events (**Figure 3a**). C3a was sampled from 22/32 states in the country, mostly from Mexico City (CMX), followed by southern states of Yucatán (YUC) and Quintana Roo (ROO; **Supplementary Figure 4, Supplementary Data 2**). The MRCA for C3a dates to late February 2021, showing a persistence of three months (earliest collection date: 02/03/2021, latest collection date: 28/06/2021). Within C7a, ~70% of the genomes were sampled from 20/32 states of the country (mostly represented by the southern state of Tabasco; TAB), followed by the norther-eastern state of Tamaulipas (TAM; **Supplementary Data 2**). As for the C3a, the MRCA node for C7a dates to late February 2021, showing a persistence of four months (earliest collection date: 10/03/2021, latest collection date: 05/07/2021).

- P.1

The P.1 lineage was first detected in Brazil during October 2020 [47], after which it diverged into >20 sub-lineages circulating in different countries[19]. Relevant to the epidemic in Mexico, the P.1.17 virus sub-lineage was sampled mostly from the USA (66% of all sequences) and Mexico (29% of all sequences; https://cov-lineages.org/) [19], again keeping in mind the sequencing bias across geographic regions. We detected at least 13 P.1 sub-lineages in the country, with the majority of genomes assigned to the P.1.17 sub-lineage (66%), and to a lesser extent to the parental P.1 lineage (25%) [33]. As our dataset comprises genomes assigned to the P.1 and descending sub-lineages, it is henceforth referred here as a P.1+. The earliest P.1+ genome from Mexico was collected in January 2021 (Mexico/JAL-InDRE_245/2021-01-28) and the latest in November 2021 (Mexico/ROO_IBT_IMSS_4502/2021-11-19). Cumulative data shows that genome sampling frequency for the P.1+ peaked around June 2021, with almost no detection after September 2021. Most of the genome sampling corresponds to the southern region of the country, represented by the states Yucatan and Quintana Roo (YUC and ROO; **Figure 3b**). As for the B.1.1.7, the P.1+ showed

an overall lower genome sampling frequency (of 25%) relative to the other lineages studied here, with spread coinciding with a decreasing number of cases following the second wave of infection in the country (**Figure 1b)** [31–33].

Phylogenetic analysis revealed a minimum number of 126 introduction events into Mexico (95% HPD interval = [120-132]; **Figure 3b**). We identified two well-supported clades named here C1_P1 (corresponding to P.1) and C1_P1_17 (corresponding to P.1.17; **Figure 3b, Supplementary Data 2**). Genomes within C1_P1 were mostly collected from the central region of the country (>40% of the sequences from Mexico City and the State of Mexico; CMX and MEX), and directly descend from genomes from South America (**Supplementary Figure 5**). The MRCA of clade C1_P1 dates to March 2021, showing a persistence of seven months (earliest collection date: 07/03/2021, latest collection date: 01/10/2021). Subsequent smaller introduction events were identified for the P.1, with most MRCAs positioned closely together (referred here as clade C1_P1 MRCAs 1 and 2; **Figure 3b**).

Genomes within clade C1_P1_17 we mostly sampled from Mexico (75%), and to a lesser extent from the USA (20%). 'Mexico' genomes are positions basally, and were collected predominantly from the southern region of the country (90%, represented by the states of Quintana Roo and Yucatán, ROO and YUC; **Supplementary Figure 5**). The MRCA of C1_P1_17 dates to October 2020, corresponding to the earliest introduction event inferred in the tree. However, the long branch between the MRCA and the earliest sequence within the clade suggests a significant under-sampling, indicating a lag in detection after lineage emergence/introduction (**Figure 3b**). Considering tip dates only, the C1_P1_17 showed a persistence of five months (earliest collection date: 01/04/2021, latest collection date: 17/09/2021). As for P.1, subsequent P.1.17 introduction events were identified as smaller clusters, with their MRCAs positioned closely together (referred here as C1_P1_17 MRCAs; **Figure 3b**). Our results indicate that the P.1 parental lineage was introduced independently to the P.1.17 and from distinct geographic locations. Contrasting to the P.1 parental lineage, the P.1.17 showed a limited number of introductions but spread successfully, showing a persistence of up to five months and establishment within the southern region of the country.

- B.1.617.2

Initially detected in India during October 2020, the B.1.617.2 lineage was associated with an increase in the number of COVID cases recorded globally after March 2021, spreading globally to become

dominant [48,49]. The parental B.1.617.2 lineage further diverged into >230 descending sub-lineages (designated as the AY.X sub-lineages) that circulate(d) in different regions of the world [19,48,50]. Again, as our dataset comprises both B.1.617.2 and AY. X-assigned genomes, it is henceforth referred here as a B.1.617.2+. The first 'B.1.617.2-like' genome from Mexico was collected on September 2020 (Mexico/AGU-InDRE_FB18599_S4467/2020-09-22), followed by a sporadic genome sampling throughout January 2021 (with <10 sequences) [51]. However, lineage expansion only occurred after April 2021 (representative earliest sequence: Mexico/JAL-InDRE_FB13752_S1722/2021-04-21). By the end of August 2021, the B.1.617.2+ reached a relative frequency of >95%, coinciding with the peak of the third wave of infection recorded in the country (**Figure 1b**) [52]. Over 80 AY.X sub-lineages were detected in Mexico, with most genomes being assigned to the AY.20 (22%), AY.26 (13%), and AY.100 (5%), followed by the AY.113 and other sub-lineages (AY.62 and AY.3) [53]. All of these were initially characterized as being most prevalent within North America [54–58]. Compared to the other virus lineages studied here, genome sampling of the B.1.617.2+ lineage in Mexico displayed a more homogeneous distribution across states, associated with an enhanced genome sampling and sequencing after May 2021 (**Figure 4**).

Phylogenetic analysis revealed a minimum number of 142 B.1.617.2+ introduction events into Mexico (95% HPD interval = [125-148]), and a total lineage persistence of seven months (up to November 30th 2021). We identified six major clades (C1d-C6d), with C1d, C3d, C5d and C6d being the largest (**Figure 4, Supplementary Data 2**). At least four synchronous introduction events were identified as the earliest MRCAs dating to April (including the introduction events leading to C3d, C4d and C6d). Within the smaller clades, C2d comprises genomes from Mexico assigned to the AY.62, sampled mainly from the state of Yucatán. Clade C4d comprises genomes from Mexico assigned to the AY.3, sampled from the north, central and south of the country (**Supplementary Data 2**). Within the larger clades, C1d is composed of genomes from Mexico assigned to AY.26, sampled mostly from the north (>60%; BCS, SIN, JAL), followed by central (CMX) and south-eastern states (VER, ROO and YUC). The MRCA of C1d dates to May 2021, showing a persistence of six months (earliest collection date: 17/05/2021, latest collection date: 12/11/2021). Comparably, C3d is composed of genomes from Mexico assigned to AY.26, sampled mostly from the north (37%; SIN, BCS and SON), and to a lesser extent from central, east and southern states. The MRCA of C3d dates to April 2021, displaying a persistence of seven months (earliest collection date: 15/05/2021, latest collection date:

30/11/2021; **Figure 4, Supplementary Data 2**). Thus, C1d and C3d represent two independent introductions events of the AY.26 sub-lineage into the country.

Clade C5d is one of the largest clades identified (n=~1500), represented by genomes assigned to the AY.100 (44%), to the parental B.1.617.2 (40%), and to the AY.113 sub-lineage (12%). Within C5d, the AY.100 and B.1.617.2 genomes are separated by a central sub-cluster of AY.113-assigned genomes (**Figure 4, Supplementary Data 2**). Approximately, 70% of the genomes within C5d were sampled from Mexico (mostly assigned to the AY.100 and AY.113), and 30% from the USA (mostly assigned to the B.1.617.2). Genomes from Mexico are positioned basally and distally, and were sampled from all 32 states, but predominantly from the north, centre and south of the country (>50%; represented by CHH, DUR, NLE, CMX, MEX, CAM, YUC, TAB, CHP and ROO; **Figure 4, Supplementary Data 2**). Thus, C5d represents the most genetically and geographically diverse clade identified. The MRCA of C5d dates to May, showing a persistence of up to six months (earliest collection date: 28/05/2021, latest collection date: 29/11/2021). Finally, C6d is the second largest clade (n=~1150), composed of genomes mostly assigned AY.20 sub-lineage, mainly sampled from central region of the country (>60%; represented by CMX, MEX, MOR, MIC and HID), suggesting a restricted geographic distribution for this transmission chain [59]. The MRCA of C6d dates to April, displaying a persistence of seven months (earliest collection date: 06/05/2021, latest collection date: 30/11/2021; **Figure 4**).

- Spread of the B.1.617.2 lineage

Being the largest clades, we further explored viral spread for the C5d and C6d under a phylogeographic approach (see Methods section 4). For C5d, viral spread within the country is likely to have occurred from the south (represented by the states of Chiapas and Campeche; CHP and CAM) into the rest of the country (**Figure 4**). Well-supported transitions (scored under a with a BFR>100 and a PP>.90, **Supplementary Table 1**) were mostly inferred from the southern state of Campeche (CAM) into central and northern states, and subsequently from the northern state of Chihuahua (CHH) into the central and northern region of the country (with some bidirectionality observed). Additional well-supported transitions were observed from Baja California into Chihuahua (BCN/BCS into CHH), and from Chihuahua into the USA (arbitrarily represented by the geographic coordinates of the state of California; **Figure 4**). Contrastingly, for C6d, viral spread within the country

is likely to have occurred from the central region (represented by Mexico City, CMX) into central, northern and southern states (again with some bidirectionality observed). Additional well-supported transitions were inferred from the southern state of Chiapas into central and northern states (**Figure 4, Supplementary Table 1**). Animated visualizations of the spread of C5d and C6d across Mexico is available as **Supplementary Data 3 and 4**.

- Linking virus spread and human mobility data

Analysis of human mobility data collected between 01/01/2020 and 31/12/2021 at a national scale (see Methods section 5) revealed two peaks in human mobility observed across time (**Figure 1c**). The first occurred between February and April 2021, coinciding with the introduction and spread of the B.1.1.7 and P.1+ lineages, and with the withdrawal of the B.1.1.519. The second peak was observed between August and November 2021, coinciding with the spread of the B.1.617.2+. Increased movements (represented by the cumulative number of trips into a given state) were observed for Mexico City, followed by Jalisco, the State of Mexico, Nuevo León and Puebla, and to a lesser extent for Coahuila, Guanajuato and Veracruz (**Figure 1c**). Mean intra-state connectivity within national territory revealed intensified movements from Mexico City into the State of Mexico, Morelos, Hidalgo, Puebla, Veracruz and Jalisco, and from Jalisco into Michoacán and Guadalajara (**Supplementary Figure 6**). However, for both the C5d and C6d clades, no correlation between transitions and the mean intrastate connectivity was observed (C5d: Adjusted R-squared: 0.006577, F-statistic: 7.15 on 1 and 928 DF, p-value: 0.007628. C6d: Adjusted R-squared: 0.3216, F-statistic: 470.8 on 1 and 990 DF, p-value: < 2.2e-16), nor with the pairwise distance between states (C5d: Adjusted R-squared: 0.01086, F-statistic: 4.051 on 1 and 277 DF, p-value: 0.04511. C6d: Adjusted R-squared: 0.02296, F-statistic: 2.715 on 1 and 72 DF, p-value: 0.1038). Many of the clades identified were localized within the southern region of the country (clades C3a and C7a belonging to the B.1.1.7, C1_P1_17 belonging to the P.1.17, and C2d and C5d belonging to the B.1.617.2). Ranking connectivity between the southern region of the country (represented by the states of Yucatán, Quintana Roo, Chiapas and Campeche) and the remaining 28 states did reveal a consistently high number of bidirectional movements between CAM, CMX and VER (**Supplementary Figure 6**).

DISCUSSION

Our analyses revealed contrasting evolutionary dynamics between lineages, with some identifiable patterns. The B.1.1.222 and B.1.1.519 are likely to have originated in Mexico, with viral spread characterized by single and extended transmission chains sustained for over a year. During this time, these lineages were seeded back and forth into Mexico and the USA, remaining endemic, but never dominating across the USA. The B.1.1.222 lineage reached a maximum national frequency of 3.5% in the USA, whilst in Mexico it reached a maximum of 35% (up to October 2020). Similarly, the B.1.1.519 lineage reached a maximum national frequency of 5% in the USA (up to April 2021), whilst in Mexico it reached a maximum of 76% (up to March 2021) [38,42]. Thus, a greater number of genomes sampled from the USA compared to the numbers from Mexico (https://cov-lineages.org/), reflect sequencing disparities across countries, an important consideration for genomic epidemiology analyses [1].

The introduction and spread B.1.1.7, P.1 and B.1.617.2 lineages in Mexico was characterized by multiple introduction events resulting in a few successful extended local transmission chains, with many clades constrained to specific regions, and displaying a persistence shorter periods of time. Further similarities were observed between the P.1 and B.1.1.7, which overlapped both spatially and temporally, coinciding with a decrease in the number of cases following the second wave of infection in the country. Compared to the B.1.1.222 and the B.1.1.519 (and later to the B.1.617.2), and contrasting to what was observed for other countries (like UK, USA and Brazil) [20,47,60], the P.1 and B.1.1.7 lineages did not dominate in Mexico [32,46]. Nonetheless, the epidemiological dynamics of these VOC in the country are comparable to those observed for other regions of the world [20,47,60]. For instance, in the USA, the earliest introductions of the B.1.1.7 were synchronous to those observed in Mexico (occurring between October and November 2020), with a similar spread pattern characterized by a few extended transmissions chains, often constrained to specific states [60]. Thus, viral spread does not seem to be linked to a higher number of introduction events, but rather to the extent and distribution of successful transmission chains, with the size of clades likely reflecting virus transmissibility [61].

Increasing growth rates (*Rt;* the instantaneous reproduction number measuring how an infection multiplies [62]) for viral variants within different geographic locations are partially explained by a genetic background increasing viral fitness [20,47,60]. For instance, in the UK, the B.1.617.2 lineage sweep occurred at a growth rate of around 60% greater than for the B.1.1.7, resulting from a combination

specific mutations increasing transmissibility and immune evasion from the host population [20]. Within Mexico, the B.1.1.519 likely displayed an enhanced fitness over the previously dominating B.1.1.222. In agreement with this observation, an *Rt* of 2.9 was estimated for the B.1.1.519, compared to an *Rt* of 1.93 for the B.1.1.222 (calculated during epidemic week 2020-46, coinciding with the early expansion of the B.1.1.519 in the country [40]). As these two lineages were directly phylogenetically related, they were almost genetically identical [41]. Relative to the parental B.1.1.222, the B.1.1.519 displayed only two amino acid changes within the Spike protein: T478K and P681H [41]. Mutation T478K is located within the RBD domain, with a possible impact in antibody-mediated neutralization [63,64]. On the other hand, mutation P681H is located upstream the furin cleavage site within an epitope signal hotspot [65] and may potentially enhance viral cell entry [66], reduce antibody-mediated recognition [65], and confer Type I interferon resistance [67].

We speculate that at least one of these mutations may have contributed to the dominance of the B.1.1.519 lineage over the B.1.1.222 by increasing the *Rt*, as has been documented for other SARS-CoV-2 subpopulations [21,22,68]. Noteworthy, the mutations observed in the B.1.1.519 were not exclusive to the lineage, as P681H emerged later and independently in the B.1.1.7 (and to a lesser extent in P.1, corresponding to 5% of all sampled genomes) [69,70]. Moreover, mutation T478K subsequently appeared in the B.1.617.2 [63,66,67]. In this scenario, we propose that a somewhat 'shared' genetic background between the B.1.1.519 and the B.1.1.7 (represented by mutation P681H) may have limited the spread of this VOC in Mexico. Although the impact of specific mutations on viral fitness would need to be assessed experimentally, current data derived from the natural virus population evidences that amino acid changes observed at site 681 of the Spike protein have been predominantly observed in VOCs, and are likely to yield an evolutionary advantage [63,66,67,71–73].

As for other regions of the world, lineage replacement dynamics during the first year of the epidemic in Mexico were probably driven by increased virus transmissibility. However, lineage establishment was likely to be shaped by the changing immune landscape of the local host population [74]. Relatively constant exposure levels to widespread and genetically similar virus subpopulations for extended periods of time (represented by the B.1.1.222 and the B.1.1.519 lineages), may have yielded consistently increasing immunity levels in a somewhat still naïve population (assuming a lower infection attack rate at that time). As more genetically divergent virus lineages were introduced and began to spread (the P.1 and B.1.1.7 lineages, and later the B.1.617.2), this resulted in a shift in the

local immune landscape, impacted by a virus genetic background prompting (at least a partial) evasion of the existing immune responses. In Mexico, a vaccination rate of >50% (reflecting the proportion of the population immunized with at least two doses) was only reached after December 2021 [29,75], suggesting that immunity levels in the population depended mostly on virus pre-exposure levels. By December 2020, a nationwide representative seroprevalence was estimated to be of ~33.5% [76,77].

Differences in the proportion of genomes sequenced across states did not always mirror the geographic distribution and extension of the transmission chains identified, but are likely reflecting an increasing sampling and sequencing intensity through time and space. Many clades identified were distributed within the south region of the country, suggesting this area has played a key role in the spread of SARS-CoV-2, comparable to observations made for other viral epidemics in Mexico (Gutierrez *et al.*, *in preparation*). Although geographic distances and human mobility trends at state level resolution did not correlate with the spread pattern of clades C5d and C6d, connectivity measures between the southern region and Mexico City do mirror some of the transitions observed. Mobility network analyses were also consistent with decrease in the number cases following epidemiological peaks (as observed for the second and third wave of infection in the country). Thus, fluctuating human mobility patterns likely reflect changes in the colour-coded system used to regulate restrictions leveraged by the risk of infection (including travel), applied at a state level [78].

As geographic distances and human mobility within the country are not potential predictors of viral spread, the patterns observed are most likely to be explained (at least partially) by both terrestrial and aerial movements across borders. Nonetheless, determining the geographic origin of introduction events is limited by genome sampling biases both at a global and local scale [79,80]. Such biases also affects the viral spread reconstructions we present, likely to be impacted by *i*) an uneven genome sampling across all Mexico states, by *ii*) an uneven sampling of foreign locations at a regional level, and by *iii*) a poor viral genome representation for many countries (*i.e.*, Central and South America) [51,81]. Taking this into consideration, it has been hypothesized that the introduction and spread of SARS-CoV-2 in Mexico would be strongly linked to mobility between Mexico and the USA (for an example, see [46]). Although human movements across these countries have indeed contributed to spread of some lineages (clearly for the B.1.1.222 and the B.1.1.519), some of the viral diffusion patterns observed across national territory are more likely to be congruent with human mobility linked

to migration routes from South and Central America into Mexico. This raises the question of the potential role of irregular migration on virus dispersal across countries, and further highlights the need of using multiple sources for human mobility data across borders (such as mobile-usage, in addition to air traffic) to inform phylogeographic analyses [82–85].

METHODS (1592/3000 WORDS)

1. Data collation and initial sequence alignments

Global genome datasets assigned to each PANGO lineage [10] under investigation (B.1.1.222, B.1.1.519, B.1.1.7, P.1 and B.1.617.2) were downloaded with their associated metadata from the GISAID platform as of November 30th 2021 [51,86]. The total number of sequences retrieved sampled globally for each virus lineage were the following: B.1.1.222 = 3,461, B.1.1.519 = 19,246, B.1.1.7 = 913,868, P.1 = 87,452, and B.1.617.2 = 2,166,874. This also included the virus genome sequences available from Mexico up the sampling date of this study. Sampling date represents the peak for B.1.617.2 frequency in Mexico before the introduction of 'Omicron' into the country [30,31]. Sequences were further excluded if they displayed incomplete collection dates, and/or if >1000 nt shorter than full genome length, and/or if showing >10% of sites coded as ambiguities (including N or X). Individual datasets were then processed using the Nextclade pipeline to filter sequences according to sequence quality [87]. In addition, a set of the earliest SARS-CoV-2 sequences sampled from 2019-2020 (including reference sequence Wuhan-Hu-1, GenBank accession ID: MN908947.3), and a set of viral genomes representing early 'Pango' diversity sampled up to 31/05/2020 were added for rooting purposes (https://github.com/BernardoGG/SARS-CoV-2_Genomic_lineages_Ecuador). Output datasets were mapped to the reference sequence Wuhan-Hu-1 (GenBank: MN908947.3) using Minimap2 [88] to generate whole genome alignments. The main viral ORFs (Orf1ab and S) were extracted to generate reduced-length alignments of approximately 25,000 bases long, comprising only the largest and most phylogenetically informative coding genome regions, to exclude smaller ORFs, UTRs, and short intergenic sequences.

2. Migration data and phylogenetically-informed subsampling

To provide an overview for global introductory events into Mexico as a proxy for dataset reduction, we used the Google COVID-19 Aggregated Mobility Research Database, describing anonymized relative

human mobility flow into different geographical regions based on mobile data usage [89,90]. For any given dataset, all 'non-Mexico' sequences are sorted according to their location, selecting only the top 5 countries representing the most intense human mobility flow into Mexico. Then, 'Mexico' sequences are subsampled to ~4,000 in proportion to the total number of cases reported in the country across time (corresponding to epidemiological weeks) according to publicly accessible epidemiological data [91]. This enables a homogeneous epidemiological and temporal representation of genomes. In case of a given lineage reporting sub-lineages, datasets are further reduced by selecting the top 5 sub-lineages that circulate(d) within the country. For 'globally sampled sequences', datasets are further reduced randomly to an approximate 1:1 ratio relative to the number of 'Mexico' sequences (keeping sequences with the earliest and latest collection dates sampled both from Mexico and globally). This migration-informed approach, coupled with balancing the number of sequences from different countries, aims to mitigate the effects of geographical over-representation impacting phylogeographic analyses, in which clades tend to not segregate fully, and certain regions may appear as more frequent seeding sources than they are in reality [1].

For each dataset, a preliminary Maximum Likelihood (ML) tree is inferred using IQ-TREE (command line: iqtree -s -m GTR+I+G -alrt 1000) [92]. The pipeline then uses a modified version of Treemmer v0.3 (https://github.com/fmenardo/Treemmer/releases) to reduce the size and redundancy of the resulting ML trees with a minimal loss of diversity [93]. Subsampling is based on phylogenetic clustering patterns, reducing the noise derived from clonal and phylogenetically overrepresented sequences. For this, the -lm command is initially used to protect 'Mexico' sequences and those added for rooting purposes. During the pruning iterations, the -pp command is then used to protect 'Mexico' clusters and pairs of 'non-Mexico' sequences that are immediately ancestral or directly descending from these. This results in reduced datasets that render local computational analyses feasible, in which clades may appear to be smaller relative to the raw counts of genomes publicly available, but reflect the sampled viral genetic diversity. Datasets are used for re-estimating ML trees as described, to be then inputted for a time-scaled phylogenetic analysis (see Methods section 4). Plots representing genome data distribution before and after implementing our subsampling approach are available in the **Supplementary Figure 4**. The pipeline is publicly accessible at (https://github.com/rhysinward/Mexico_subsampling).

3. Dataset construction

Given the reduced size of the original B.1.1.222 dataset, all sequences retained after initial quality filtering were used for analyses. This resulted in a 3,849-sequence alignment (including 760 genomes from Mexico) used for ML tree inference using IQ-TREE (iqtree -s -m GTR+I+G -alrt 1000; **Supplementary Data 1**). The resulting tree was further inputted for a time-scaled analysis (see Methods section 4). All other datasets (B.1.1.519, B.1.1.7, P.1 and B.1.617.2) were processed under the pipeline described above to render informative datasets for phylogeographic analysis (see Methods section 2 and 4). The B.1.1.519 final dataset resulted in a 5,001-sequence alignment, including 2,501 genomes from Mexico. The B.1.1.7 final dataset resulted in a 7,049-sequence alignment, including 1,449 genomes from Mexico. The P.1 final dataset resulted in a 5,493-sequence alignment, including 2,570 genomes from Mexico. The B.1.617.2 final dataset resulted in a 5,994-sequence alignment, including 3,338 genomes from Mexico (**Supplementary Data 1**). Individual datasets were then used for ML tree inference as described, with the resulting trees used as input for time-scaled analyses (described in Methods section 4).

4. Time-scaled analysis

Output ML trees were assessed for temporal signal using TempEst v1.5.3 [94], removing outliers and re-estimating trees when necessary. Trees were then time-calibrated informed by tip sampling dates using TreeTime [95] (command line: treetime -aln --tree --clock-rate 8e-4 --dates --keep-polytomies --clock-filter 0). Due to a low temporal signal, a fixed clock rate corresponding to a reported virus evolutionary rate estimate of 8×10^{-4} substitutions per site per year was used [96,97]. Root-to-tip regression plots for the ML trees (prior to time calibration and excluding rooting sequences) are available in the **Supplementary Figure 3**. In order to investigate viral introductions into Mexico, the time-calibrated trees were used as input for a discrete trait analysis (DTA, or 'discrete phylogeographic inference') using BEAST v1.10.4 to generate maximum clade credibility (MCC) trees [98–100]. Using fixed 'time-calibrated' tree as an input for DTA in an effective way of circumventing the restrictions of computationally-expensive analyses on large datasets [98]. However, although this approach allows inferring dates and number for introduction events into the study area, it does not consider the uncertainty associated with phylogenetic inference (*i.e.*, the dates of inferred MRCAs do not come with a credibility intervals). Introduction events into the country are associated with the most

recent common ancestor (MRCA) node of each 'Mexico' clade. Following a similar strategy as described in du Plessis et al.[3] 'Mexico' clades were identified as those composed by a minimum of two sister 'Mexico' sequences directly descending from another 'Mexico' sequence. For all introduction events identified in the MCC trees, the mean and associated HPD interval were assessed.

Analyses for the B.1.1.7 and the P.1 and B.1.617.2 datasets were performed to estimate the number of introduction events into Mexico from other (unknown) geographic regions, and only two locations were considered: 'Mexico' and 'other'. For the B.1.1.222 and B.1.1.519 dataset, we estimated the number of transitions between Mexico and the USA, thus considering three distinct geographic locations: 'Mexico', 'USA' and 'other'. Each Monte Carlo Markov Chain (MCMC) was run for 10^6 iterations, sampling every 10^3 iterations. To assess if sufficient effective sample size values (*i.e.,* ESS>200) were associated with the estimated parameters, we then inspected MCMC convergence and mixing using the program Tracer 1.7 [101]. To explore viral spread across the country, two additional DTAs were performed within each of the largest monophyletic clades identified within the B.1.617.2+ tree (C5d and C6d, see Results section). These additional DTAs were based on the definition of 33 distinct sampling locations (all 32 states from Mexico + 'other' for genomic sequences sampled from outside the country). Visualization of viral spread patterns was performed using SpreadViz (https://spreadviz.org/home), an updated web implementation of the Spatial Phylogenetic Reconstruction of Evolutionary Dynamics software SpreaD3 [102], also used to estimate Bayes Factor Rate (BFR) values to identify well-supported transitions between locations [100] (**Supplementary Table 1**).

5. Human mobility data analysis and exploring correlations with genomic data

Human mobility data used for this study derived from anonymized mobile device locations provided by the company Veraset collected between 01/01/2020 and 31/12/2021 within national territory. The source dataset includes anonymized identifiers for mobile devices, geographical coordinates (latitude and longitude) and a timestamp. The dataset was used to construct aggregated intra-state mobility networks, where nodes are defined as each of the 32 states from the country, whilst (weighed and directed) edges represent the normalized volume of observed trips between nodes [103]. The resulting networks were then used to quantify the number of cumulative trips from any state into a given

specific state across time, the geographic distances among states, the mean intrastate connectivity observed between April 2021 and November 2021 (corresponding to the expansion period for the B.1.617.2 lineage, see **Figure 4b**), and for ranking connectivity between the southern region of the country (represented by Yucatán, Quintana Roo, Chiapas and Campeche) and the remaining 28 states (see **Supplementary Figure 8,** matrixes available as **Supplementary Data 5**). The connectivity measure was defined as the sum of the weights for edges that go from any given node into other node(s), reflecting the number of trips in any direction. We then used the 'PhyCovA' software tool (https://evolcompvir-kuleuven.shinyapps.io/PhyCovA/) to perform preliminary analysis for exploring the human mobility data from the country as a potential predictor of viral transition among locations [104]. 'PhyCovA' was chosen as an explanatory approach over a fully-integrated GLM implemented in the Bayesian BEAST framework, as the last one would imply a high computational burden related to our datasets [99].

DATA AVAILABILITY

Virus genome IDs and GISAID accession numbers for the sequences used in each dataset are provided in the **Supplementary Data 1** file. All genomic and epidemiological data supporting the findings of this study is publicly available from GISAID/GenBank, from the Ministry Of Health Mexico[105], and/or from the 'Our world in data coronavirus pandemic web portal [29]. For the GISAID data used, the corresponding acknowledgements table is available on the 'GISAID Data Acknowledgement Locator' under the EPI_SET_20220405qd and EPI_SET_20220215at keys [51]. Our bioinformatic pipeline implementing a migration data and phylogenetically-informed sequence subsampling approach is publicly available at https://github.com/rhysinward/Mexico_subsampling.

AUTHOR CONTRIBUTIONS

HGCS, LD, BG, RPDI, SD, and MEZ performed research and analysed data. RPDI developed the bioinformatic pipeline, whilst RPDI, NMV and CB processed data. MK, BG and RPDI, together with the Mobility Team in Mexico [MHR, AM, MF, OF, PG, GOA, GAJ] performed the analysis of human mobility data integrated with genomic data. Other members of CoViGen-Mex and ACG, BT, SZ, SL, CFA, AL and MEZ contributed to the initial experimental design by leading evolutionary analyses part of the duties of the consortium. OGP and SD contributed to revising the methodological approach.

MEZ supervised and coordinated data analysis. MEZ wrote the manuscript, with contributions and comments from all authors.

COMPETING INTERESTS

The authors declare no competing interests.

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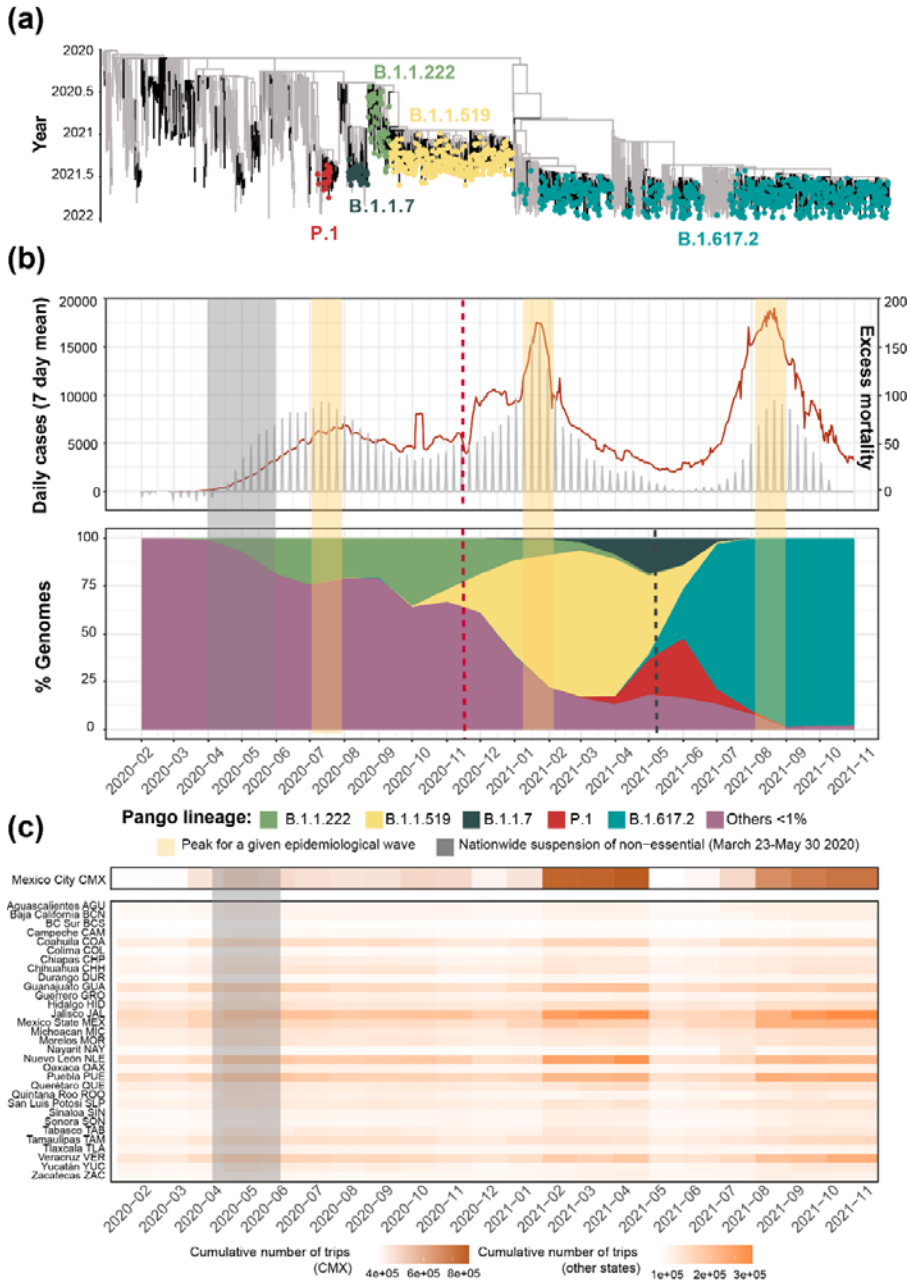
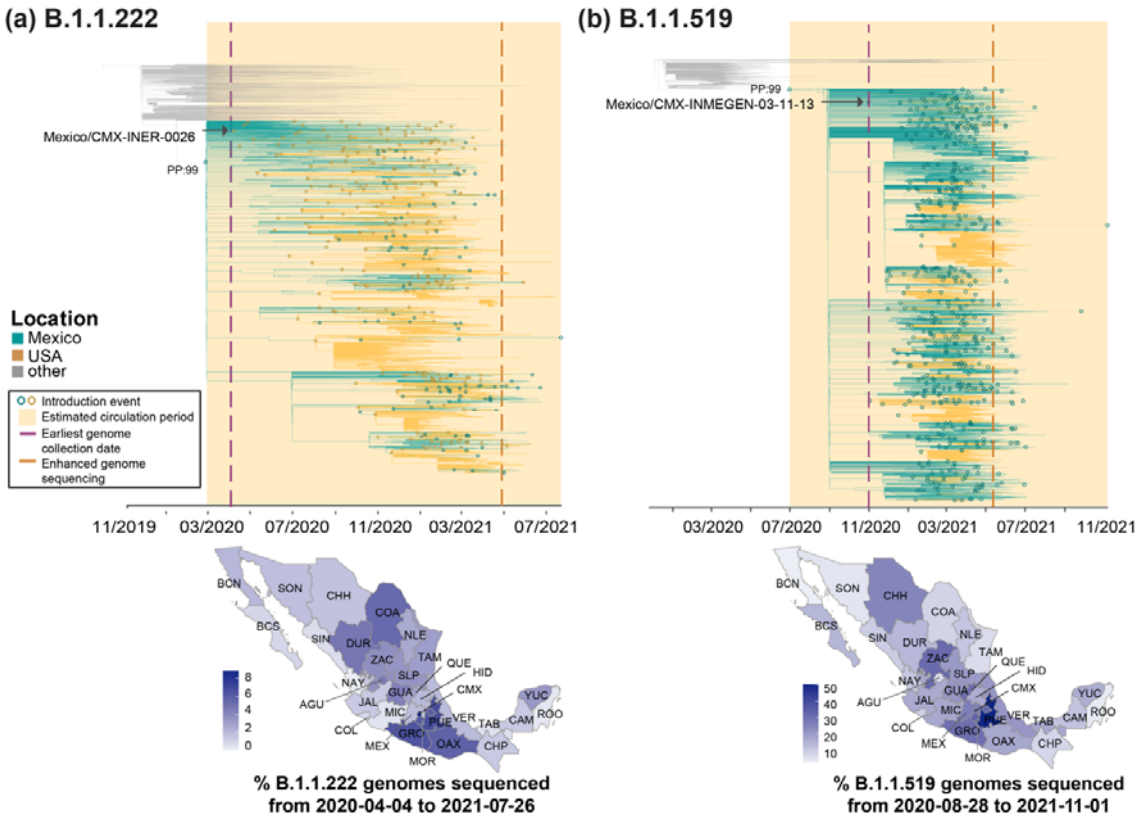
FIGURES

Figure 1. Overview of the SARS-CoV-2 epidemic in Mexico



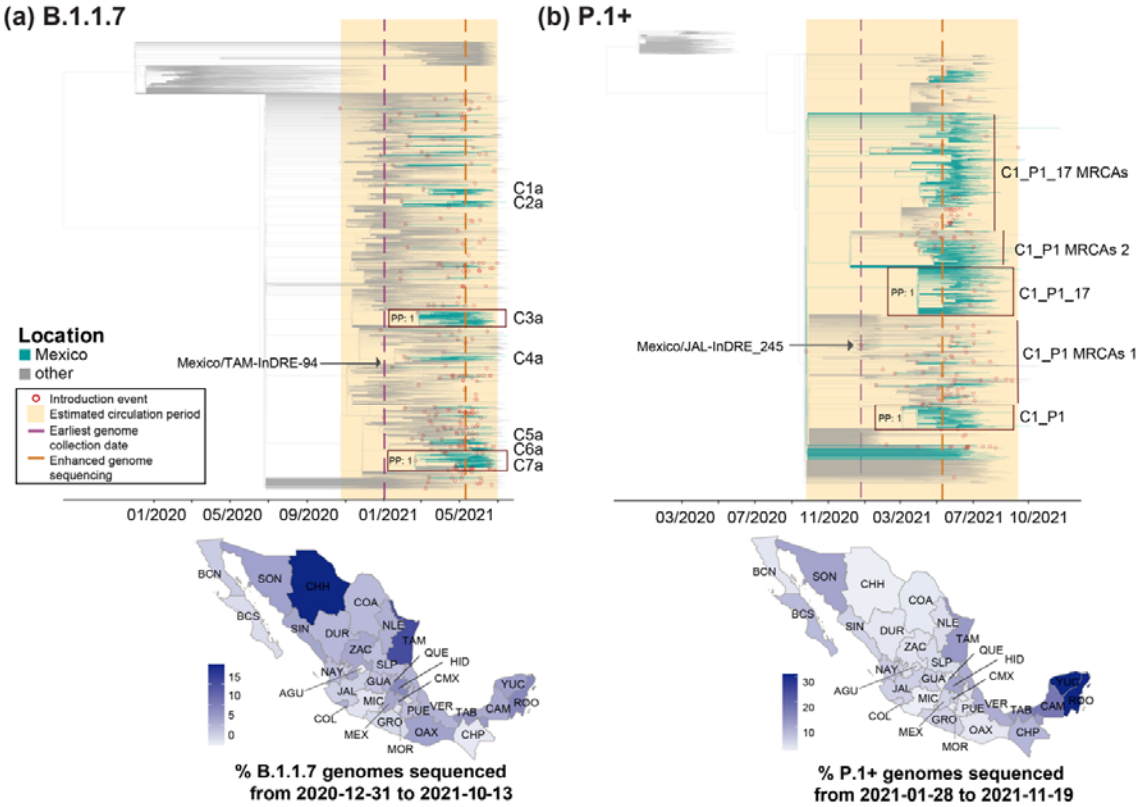
(a) Time-scaled phylogeny for representative viral genomes from Mexico within a global context, highlighting the positioning of the B.1.1.222, B.1.1.519, B.1.1.7, P.1 and B.1.617.2 virus lineages. (b) The epidemic curve for COVID-19 in Mexico from January 2020 up to November 2021, showing the average number of daily cases (red line) and the associated excess mortality (grey line). The peak for the first, second and third waves of infection are highlighted in yellow shadowing, whilst the lower panel represents the percentage of SARS-CoV-2 genomes from Mexico assigned to distinct 'Pango' lineages within the given timeframe. Lineage B.1.1.222 is shown in light green, B.1.1.519 in yellow, P.1 in red (Gamma), B.1.1.7 (Alpha) in dark green, and B.1.617.2 (Delta) in teal. Other lineages displaying a lower sampling frequency are jointly shown in purple. The time period for the implementation of non-pharmaceutical interventions at national scale is highlighted in grey shadowing. (c) Heatmap displaying the volume of trips into a given state from any other state recorded from January 2020 up to November 2021 derived from anonymized mobile device geolocated and time-stamped data. The dashed red line corresponds to the start date national vaccination campaign (December 2020), whilst the dashed black line represents the implementation date of a broader viral genome sampling and sequencing scheme for the surveillance of SARS-CoV-2 in Mexico (after May 2021).

Figure 2. Time-scaled phylogenetic analyses for the B.1.1.222 and B.1.1.519 lineage



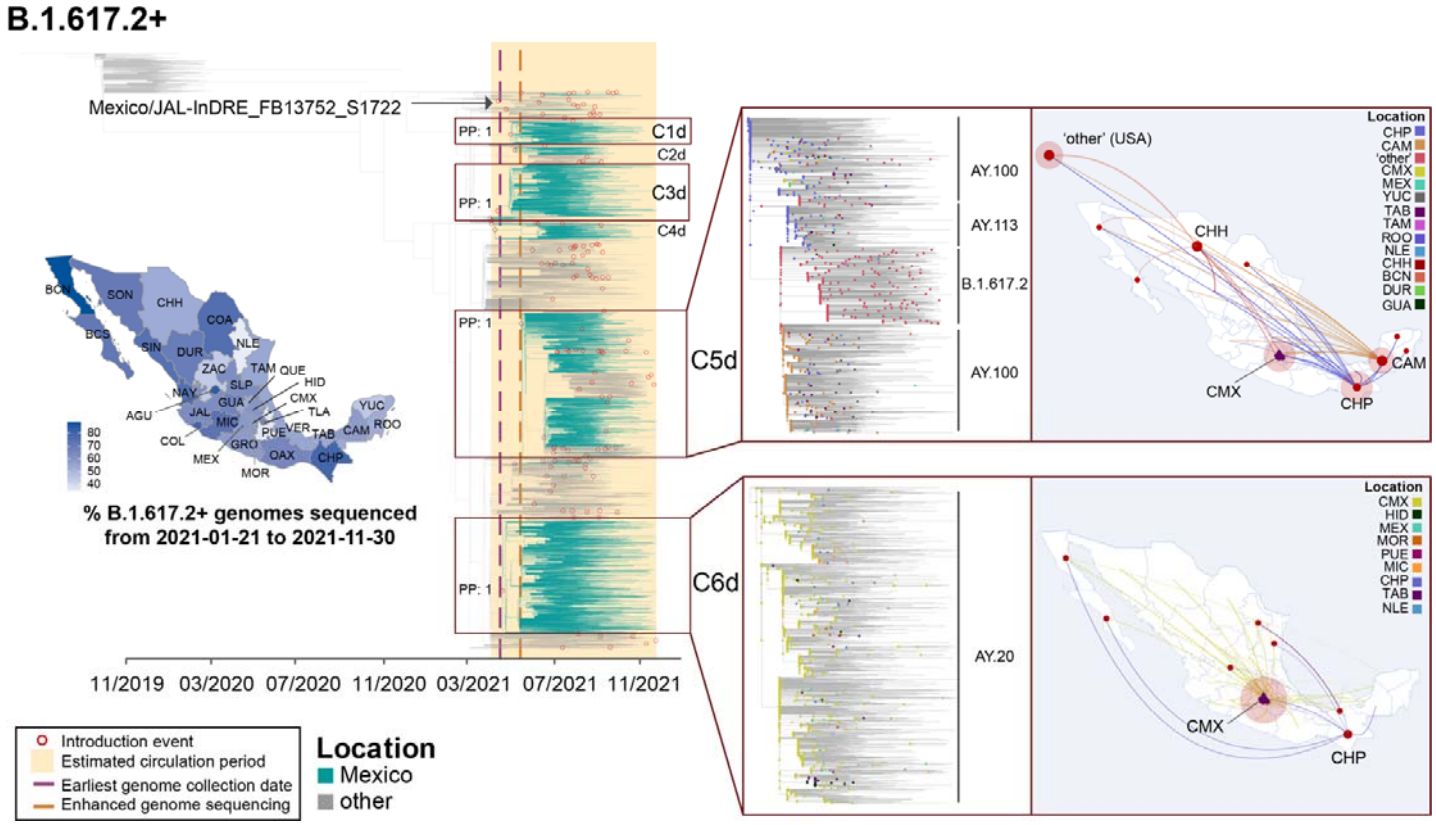
Maximum clade credibility (MCC) trees for the (a) B.1.1.222 and (b) B.1.1.519 lineages, in which the main clades corresponding to distinct introduction events into Mexico are highlighted. Nodes shown as outline circles correspond to the most recent common ancestor (MRCA) of clades resulting from a distinct introduction event into Mexico (in teal) or the USA (in ochre). The estimated circulation period in Mexico for a given lineage is highlighted in yellow shadowing. The dashed purple line represents the collection date for the earliest lineage-assigned genome sampled from Mexico, with its position indicated with an arrow. The dashed yellow line represents the implementation date (May 2021) of a broader viral genome sequencing scheme for the surveillance of SARS-CoV-2 in Mexico. Below, map graphs show the cumulative proportion of viral genomes from Mexico assigned to each virus lineage relative to the total number of genome sequences reported for any given state (taken from GISAID, corresponding to raw data before subsampling).

Figure 3. Time-scaled phylogenetic analyses for the B.1.1.7 and P.1+ lineages



Maximum clade credibility (MCC) trees for the (a) B.1.1.7 and the (b) P.1+ B.1.617.2 lineages, in which major clades identified as distinct introduction events into Mexico are highlighted. Nodes shown as red outline circles correspond to the most recent common ancestor (MRCA) of clades resulting from a distinct introduction event into Mexico. The estimated circulation period for a given lineage is highlighted in yellow shadowing. For each panel, the dashed purple line represents the collection date for the earliest lineage-assigned genome sampled from Mexico, with its position within the tree indicated with an arrow. The dashed yellow line represents the implementation date (May 2021) of a broader viral genome sampling and sequencing scheme for the surveillance of SARS-CoV-2 in Mexico. Below, map graphs show the cumulative proportion of viral genomes from Mexico assigned to each virus lineage of interest relative to the total number of genome sequences reported for any given state (taken from GISAID, corresponding to raw data before subsampling).

Figure 4. Time-scaled and phylogeographic analysis for the B.1.617.2+ lineage



Maximum clade credibility (MCC) tree for the B.1.617.2+ lineage, in which major clades identified as distinct introduction events into Mexico are highlighted. Nodes shown as red outline circles correspond to the most recent common ancestor (MRCA) of clades resulting from a distinct introduction event into Mexico. The estimated circulation period is highlighted in yellow shadowing. The dashed purple line represents the collection date for the earliest lineage-assigned genome sampled from Mexico, with its position within the tree indicated with an arrow. The dashed yellow line represents the implementation date (May 2021) of a broader viral genome sampling and sequencing scheme for the surveillance of SARS-CoV-2 in Mexico. On the left, a map graph sows the cumulative proportion of sequenced viral genomes from Mexico assigned as B.1.617.2+, relative to the total number of genome sequences reported for any given state (taken from GISAID, corresponding to raw data before subsampling). On the right, a zoom-in to the C5d and C6d clades shows sub-lineage composition and the inferred location for nodes. The geographic spread of these clades across Mexico is shown from the inferred discrete phylogeographic analysis (see Methods section 4). Viral lineage transition events between Mexican states are represented by curved lines coloured according to sampling location, showing only well-supported transitions (Bayes factor rate >100 and a posterior probability >0.9). Bayes factor rate values are all reported in the Supplementary Table 1.

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