Lessons learnt from 288 COVID-19 international cases: importations over time, effect of interventions, underdetection of imported cases

[Report #5] [Report #4] [Report #3] [Report #2] [Report #1]

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23/02/2020 (DATA UP TO 14/02/2020)

SUMMARY

288 cases have been confirmed out of China from January 3 to February 13, 2020. We collected and synthesized all available information on these cases from official sources and media. We analyzed importations that were successfully isolated and those leading to onward transmission. We modeled their number over time, in relation to the origin of travel (Hubei province, other Chinese provinces, other countries) and interventions. We characterized importations timeline to assess the rapidity of isolation, and epidemiologically linked clusters to estimate the rate of detection. We found a rapid exponential growth of importations from Hubei, combined with a slower growth from the other areas. We predicted a rebound of importations from South East Asia in the upcoming weeks. Time from travel to detection has considerably decreased since the first importation, however 6 cases out of 10 were estimated to go undetected. Countries outside China should be prepared for the possible emergence of several undetected clusters of chains of local transmissions.

INTRODUCTION

Twenty-six countries worldwide have declared cases of the novel coronavirus, COVID-19, as of February 20, 2020[1]. Only China so far registered a widespread epidemic[2], and authorities have implemented massive intervention measures to curtail it[3]. Outside China, affected countries are facing importations of cases and clusters of local transmission[1,4,5] Border controls have been reinforced in many countries, and active surveillance has been intensified to rapidly detect and isolate importations, trace contacts and isolate suspect cases[6,7].

The effectiveness of such measures, however, critically depends on COVID-19 epidemiology and natural history[8,9], as well as the volume of importations[6]. The presence of an incubation period, during which infected individuals carry on their usual activities (including travel), is a major challenge for screening controls at airports[8]. Moreover, mild non-specific symptoms and transmission before the onset of clinical symptoms[2,10] may compromise infection control measures for importations and onward transmissions[9]. There is concern that imported cases may have gone undetected and contribute unknowingly to the global spread of the disease[11–15].

Here we systematically collected and analyzed data on 288 COVID-19 confirmed cases outside China. We analyzed importations that were successfully isolated and those leading to onward transmission, characterizing their case timeline. We developed a statistical model to nowcast trends in importations and quantify the proportion of undetected imported cases.

METHODS

Data collection and synthesis. We collected all international cases confirmed by official public health sources in the period from January 3 to February 13, 2020. Case history was reconstructed by searching the scientific literature, official public health sources, and news. Case history included: dates of travel and symptoms onset, date of COVID-19 confirmation, date of hospital admission, date of case isolation, travel history, epidemiological link with other cases, hospitalization history. International cases included imported cases, secondary cases out of China, and repatriations. Cases from cruises were not considered here. Information was extracted by LDD and EO and checked by MM. The full database, along with the database describing clusters, were made publicly available[16].

Descriptive analysis. For imported cases with full information on the timeline of events, we computed the average duration from travel to onset, from travel to hospitalization, and from hospitalization to reporting. We used analysis of variance to compare groups of imported cases that generated or did not generate local transmissions. We extended the analysis to all imported cases combining cases with full and partial information on the timeline. We used the analysis of variance and multiple imputation for the missing data. Results were combined using Rubin's approach[17].

Modeling and predicting importations. We modeled the total number of imported cases out of China over time accounting for date of travel, delay in reporting, and source areas.

We distinguished between three different sources: Hubei province (H), the rest of China (C), other countries (O). We modeled imported cases over time as a piecewise exponential function depending on the source and on travel restrictions in place. We assumed a different situation in Hubei province and the rest of the world due to the level of awareness in the different phases of the outbreak. The exponential functions are defined as follows:

$$I_{S,t} = \begin{cases} I_S^{pre} * e^{r_S^{pre} t} & t \le T_S \\ I_S^{post} * e^{r_S^{post} t} & t > T_S \end{cases} \quad , \quad S = H, C$$

$$I_{O,t} = I_O * e^{r_O\, t},$$

where r_H^{pre} is the growth rate of cases coming from Hubei, and r_C^{pre}, r_O^{pre}, with $r_C^{pre} = r_O$, the growth rates of cases coming from the rest of China and other countries, respectively. Travel restrictions were modelled by assuming a discontinuity in the growth rate. For Hubei, we assumed the growth rate to change from r_H^{pre} to r_H^{post} after the travel ban of January 23, 2020 (indicated with T_H); for the rest of China, we assumed an analogous change from r_C^{pre} to r_C^{post} after January 29, 2020 (T_C), date of first flight cancellations[18]. No change was considered for the other countries (r_O constant over time), as no restrictions of travel were established towards these countries. The scale parameters of the exponential functions ($I_H^{pre}, I_H^{post}, I_C^{pre}, I_C^{post}, I_O$) were assumed to be different among the three sources, to account for different traveling volumes and dates of beginning of importations.

We modelled the time τ from importation to detection of a case with a gamma distribution, $g_t(\tau)$, conditioned to the date of case importation, t. $g_t(\tau)$ was assumed to have constant coefficient of variation (SD/mean) achieved by a constant shape parameter and a rate parameter varying smoothly in time to capture change in surveillance efficiency.

We used a Bayesian framework to fit the model to imported cases by origin, travel date, and confirmation date. Cases with partial information (e.g. missing date and/or origin of travel) were included by defining latent variables marginalized out during inference. The model was then used to nowcast imported cases two weeks in the future. All details of the analysis are reported in the Appendix.

Estimation of under-detection of imported cases. We analyzed clusters of transmission generated by imported cases (index case(s) in each cluster) to estimate undetected importations. A cluster can be seeded by more than one index case when local transmissions are epidemiologically linked to more cases traveling together (e.g. infected family members traveling together). We modelled the number of such 'cluster seeds', i.e. groups of index cases, with a multinomial distribution depending on the portion of cluster seeds of size 1 or greater than 1 (for simplicity, this was taken as 2), on the probability of detection of a seed, and on occurrence of secondary transmission. The likelihood function was a function of: the number x_1 of observed clusters with one index case; the number x_2 of observed clusters with more than 1 index cases; the number $\tilde{y}$ of detected index cases not leading to onward transmission; the number z of clusters whose index cases have not been identified; and the number w of undetected imported cases that did not generate any cluster. w can be estimated through likelihood maximization from the records of $x_1, x_2, \tilde{y}, z$.

TIMELINE OF TRAVEL-RELATED CASES

We collected 288 cases, including 163 imported cases, 109 local transmissions, 30 repatriations, and 1 case of unknown origin. Fifteen cases were classified as both imported and local transmissions, since they contracted the infection outside China and traveled to a different country once infected (ES01, ES02, GB03, GB04, GB05, GB06, GB07, GB08, KR12, KR16, KR17, KR19, MY09, TH20, TH21 in our database[16]).

Figure 1 summarizes the timeline of imported cases. Symptoms onset occurred after the travel to the destination country for almost all cases for which date of travel and of onset are available (68 out of 73, 93%). Complete information was available for 51 (31%) imported cases, with quality of information decreasing over time (Figure S1 of the Appendix).

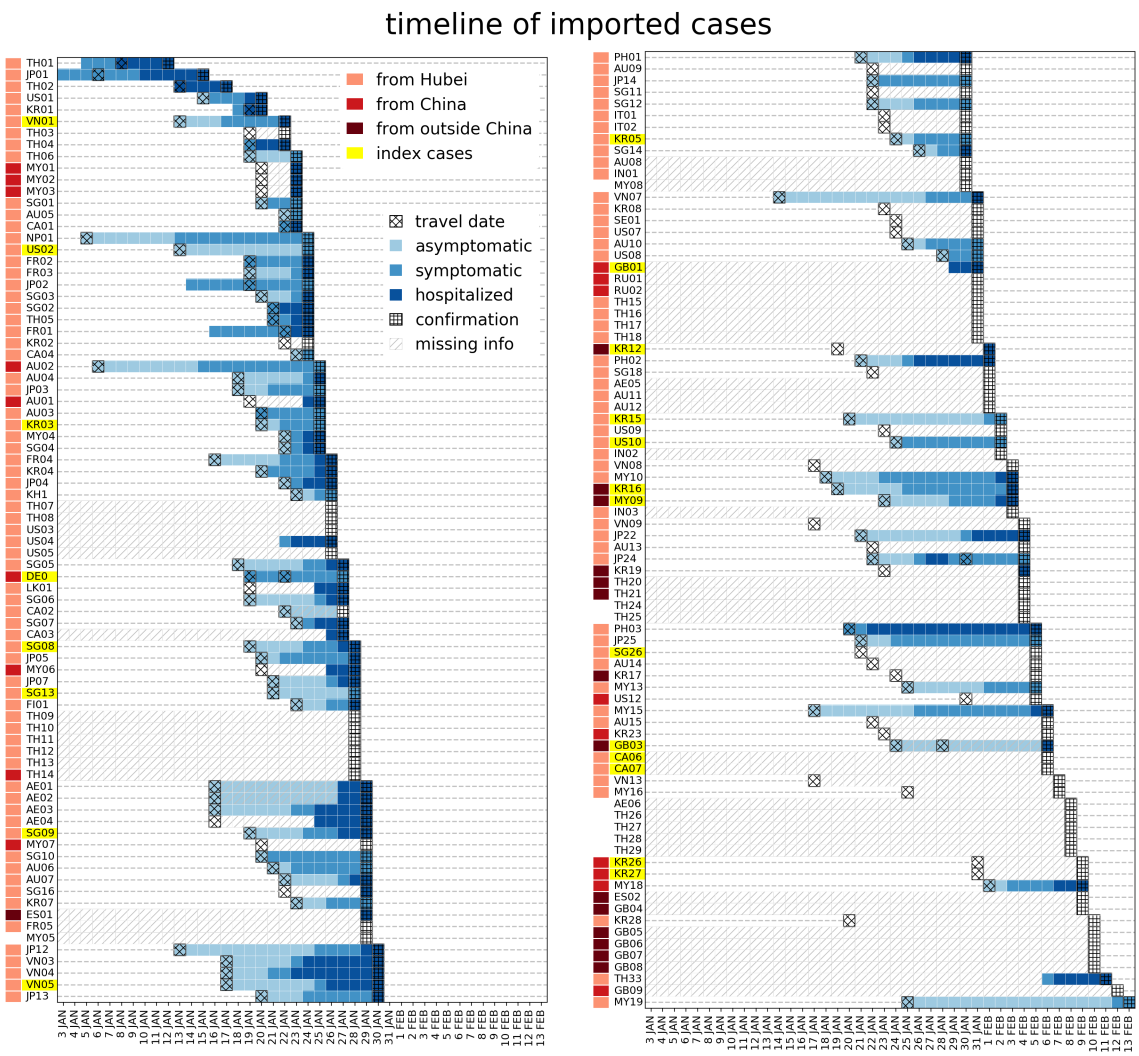

Figure 1. Timeline of importation for all imported cases.

Among imported cases with full information, the delay from travel to hospitalization was longer in cases that generated secondary transmissions (mean of 10 ± 0.97 days compared to 5.5 ± 0.67 days, p=0.003). Overall, the duration from travel to first event (whether symptom onset, or hospitalization for asymptomatic) was also longer, although the difference was not statistically significant (5.0 ± 0.9 days vs. 3.7 ± 0.5 days p= 0.08). Durations of hospitalization were instead comparable among the two groups of cases (1.5 ± 0.7 days vs. 2.6 ± 0.4 days for cases that generated or did not generate secondary transmissions, respectively). Including imported cases with missing information through imputation, we found the same trend though smaller in magnitude and not statistically significant (delay from travel to hospitalization 9.8 ± 1.2 vs. 8.3 ± 0.5 days p= 0.3; delay from travel to onset 5.8 ±1.1 vs. 4.2 ±0.5 p= 0.16, for cases that generated or did not generate secondary transmissions, respectively). This suggests that importations with missing information may be closer in characteristics to index cases leading to onward transmission.

The statistical model predicted a decrease in the average time from travel to detection from 14.5 ± 5.5 days on January 5, 2020 to 6 ± 3.5 days on February 1, 2020 (Figure 2).

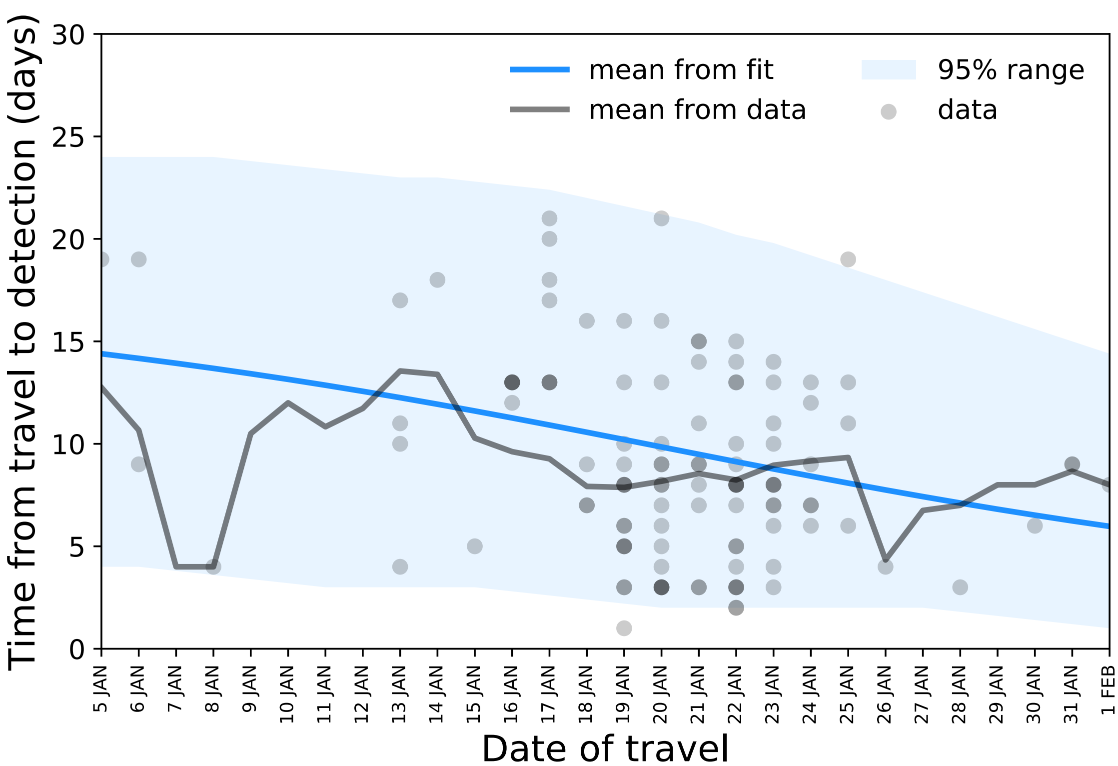

Figure 2. Delay from travel to detection as a function of the date of travel: data points, mean, and model prediction.

NOWCASTING TRAVEL-RELATED CASES

The model predicted a rapid exponential growth of importations from Hubei, with a growth rate $r_H^{pre} = 0.26$ [95% CI 0.21, 0.31], corresponding to a doubling time of 2.8 days. In comparison, the exponential growth from other territories (rest of China and countries other than China) was slow, $r_C^{pre} = r_O = 0.04$ [0.00, 0.08]. After the implementation of travel restrictions, a negative growth rate was estimated, signaling a decline in imported cases. The decline was sharp for Hubei (r_H^{post} = -0.64 [-0.85, -0.48]) and more gradual for the rest of China (r_C^{post} = -0.19 [-0.54, 0.00]).

The predicted trend of all imported cases over time is shown in Figure 3, compared with the observed data. Reported importations are predicted to remain stationary in the second and third week of February and to rise again due to the effect of transmission clusters outside China. Imported cases after February 13, 2020 are in agreement with model predictions (Fig.3).

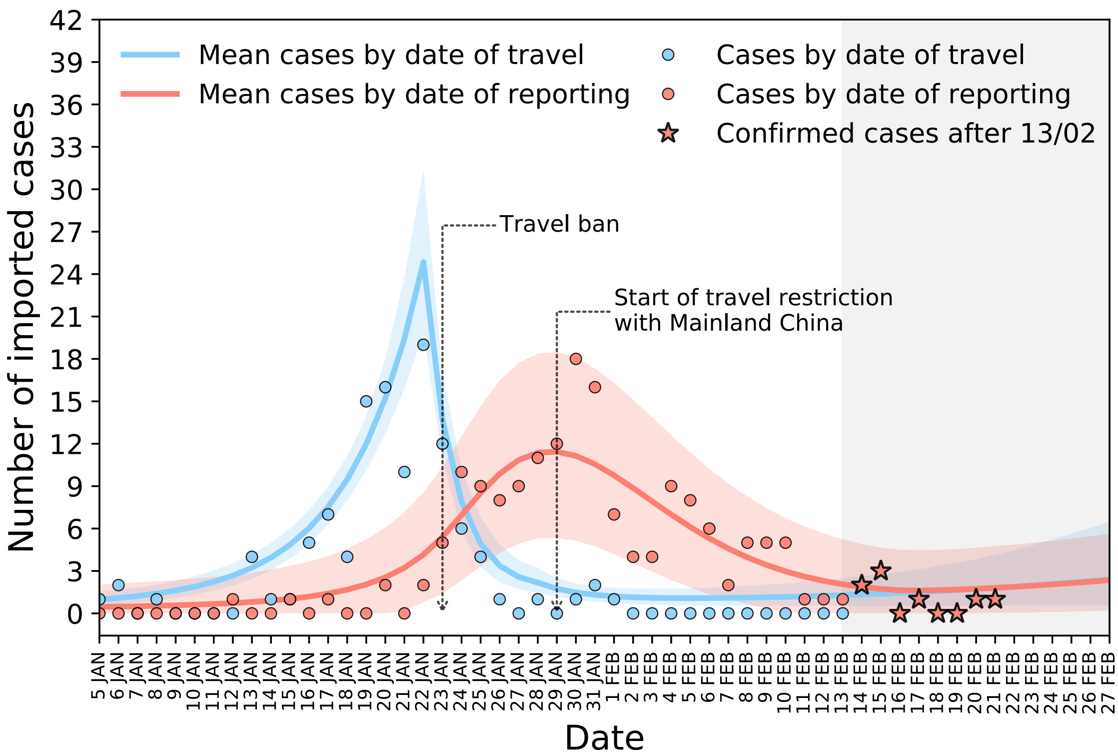

Figure 3. Number of imported cases by date of travel and of reporting: data points and model predictions.

TRASMISSION CLUSTERS OUTSIDE CHINAS

Table 1. Summary of transmission clusters according to the type of index case.

Index Case	Number of clusters	Clusters (size)
Traveller(s) identified prior to cluster detection*	15	cDE01 (16), cFR02 (12), cVN02 (7), cKR01 (5), cSG04§ (5), cKR04 (3), cMY01 (3), cSG11§ (3), cVN01 (3), cGB01 (2), cKR02 (2), cKR03 (2), cKR05 (2), cUS01 (2), cUS02 (2)
Traveller(s) not identified or retrospectively identified **	8	cSG01 (10), cSG02 (8), cJP01 (4), cCA01 (3), cKR06 (3), cTH04 (3), cFR01 (2), cJP02 (2)
Unknown***	19	cSG13 (8), cSG09 (5), cJP03 (3), cJP06 (3), cSG14 (3), cJP04 (2), cJP05 (2), cJP07 (2), cSG03 (2), cSG05 (2), cSG06 (2), cSG07 (2), cSG08 (2), cSG10 (2), cSG12 (2), cTH01 (2), cTH02 (2), cTH03 (2), cAE01(****)

§Cluster associated to two traveling cases

*The index case was identified independently from secondary transmissions

**The index case was either:

- identified retrospectively following case investigation prompted by the detection of secondary cases
- The identity was not identified; however, the cluster was linked to a specific location/circumstance visited by Chinese travellers (shop, conference, bus tour)

***No connection with other case or source of infection has been identified yet

****Insufficient information

Forty-two transmission clusters were identified out of China in the timeframe under study. Table 1 summarizes the size and country of each cluster. Clusters were grouped according to whether the index case: (i) was a traveling case identified prior to cluster detection; (ii) a traveling case not identified or identified retrospectively once the cluster was observed; (iii) completely unknown. Assuming that clusters of unknown origin were linked to one of the already observed imported cases - or, in other words, not linked to an undetected imported case - led to an estimate of 76 [49, 118] undetected imported cases. In this scenario, detected cases would amount to 65% of all imported cases. Assuming instead that all clusters of unknown origin were due to undetected imported cases increased the number of undetected cases to 225 [186, 369], i.e. detected cases would correspond to only 36% of the total.

CONCLUSIONS

As the COVID-19 epidemic in China shows effects of mitigation[2], increasingly larger clusters of infections reported outside China are raising concern that other territories may start sustaining the outbreak[4,5]. To contain it globally, identification, rapid management of cases, and contact tracing are key. The success of these response measures depends critically on the volume of importations[19] and the sensitivity of active surveillance[13,15].

We reviewed here all confirmed cases out of China from January 3 to February 13, 2020 and gathered detailed information on case history and epidemiological links. We identified salient epidemiological features, and modeled the number of importations over time. International exportations from Hubei grew rapidly, fueled by the local epidemic, up to the closure of Wuhan airport preventing further travel of cases. Exportations from other Chinese provinces and other countries grew at a considerably slower pace. This is related to the difference in the increase of cases between Hubei province, origin of the outbreak, and the rest of the affected areas[1]. Such difference is likely an outcome of the implementation of containment measures in China[3,20,21], and of the increased awareness at different phases of the outbreak[22–26] (i.e. before and after containment measures) leading to self-isolation and quarantine.

The reduced volume of exported cases worldwide following the travel ban may have given countries the time to prepare and strengthen their surveillance systems, as signaled by a reduction of the interval from travel date to detection over time.

Our model predicts that exportations will likely rise from areas outside China. The number of local transmissions is rapidly increasing in the Republic of Korea, Japan, and Singapore[27], and few importations in Asia and Europe were registered already from travelers from Japan and Singapore. For this reason, certain countries have updated the history of travel for the case definition of a suspect imported case to include additional countries in South Asia besides China[28] or banned travelers from East Asian countries[29]. ECDC and WHO currently base their case definition on travel from China only[30,31], but this may rapidly change in the next days.

Before the likely rebound of exportations, identification and isolation of possible clusters outside China remain essential to contain local transmission. The increasing reporting of clusters outside China with no known epidemiological link[1,14] raises important concerns on the possibility to contain COVID-19 epidemic worldwide. Our estimates indicate an ability of 36% to detect imported cases in countries outside China. This means that approximately 6 imported cases out of 10 have gone undetected. Previous estimates range from 27%[13] to 38%[13,15] detection rates, with variations across countries[13,15]. Ascertainment was estimated to be even lower (approximately 10%) when assessed on repatriations[31]. Here, we excluded from this analysis all repatriation events and cruises with outbreaks, as conditions for detection and identification may be different.

Underdetection may be due to several different factors including asymptomatic infections, infections with mild clinical symptoms, health-seeking behavior and declaration of travel history, case definition, and underdiagnosis. Underdetection of imported cases is likely to be higher than what we estimate here, as our analysis is conditional to the identification of clusters of cases. The current situation in Italy, with different clusters emerging in the timeframe of few hours in different areas in the North of the country[14], shows that clusters have gone undetected and epidemiological links with the index case are still missing. Countries outside China should be prepared for the possible emergence of several undetected clusters of chains of local transmissions. Surveillance efforts to track all suspect cases may become impractical if the number of cases increases too rapidly[32]. If that situation occurs, countries should be ready to step-up their response and take preparatory steps for community interventions.

ACKNOWLEDGMENTS

This study is partially funded by: the ANR project DATAREDUX (ANR-19-CE46-0008-03); the EU grant MOOD (H2020-874850); the Municipality of Paris through the programme Emergence(s). We thank REACTing (https://reacting.inserm.fr/) for useful discussions.

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APPENDIX

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