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COVID-19 : HOW TO FIND SILENT SPREADERS ?

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Abstract : The french government has presented its end of lockdown plan on Tuesday 28 April. Among the key measures, "test and isolate" all positive cases. For this purpose the french government is targeting 700,000 RT-PCR assays per week. This number has been sized up to test all new infected people each week as well as their contacts during the two days prior to symptoms. However, only clinical cases (and their contacts) are going to be teste but clinical cases represent less than 10% of all infected people. Most healthy carriers will remain invisible and - as they are also silent spreaders – require to be found. We propose here a testing strategy, combining virologic AND serologic tests, to identify most healthy carriers in a given territory. If generalized, this could make it possible to eradicate covid-19.

The french government has presented its end of lockdown plan on Tuesday 28 April. Among the key measures, "test and isolate" all positive cases : "Each new case will correspond on average to the test of at least 20 to 25 people who crossed it in the previous days. 3,000 times 25 times 7, that's 525,000 tests per week. Indeed, it has been estimated that there would still be between 1,000 and 3,000 newly infected people per day on May 11, the day set for the end of lockdown ([Salje et al.](#) See Figure 3C). The target of 700,000 tests per week would therefore guarantee the identification and isolation of most of the virus carriers and thus prevent a second epidemic wave.

Is it that true ?

The vast majority of chains of transmission are indeed invisible: half of the cases (infected subjects) are asymptomatic ([Mizumoto et al](#)); and a majority of symptomatic cases are not; so that only a small minority of cases are eventually detected in France where tests have been reserved for serious cases or fragile subjects so far : about 8% of all cases (see [Annex](#)). These clinical cases generally justify hospitalization. Consequently, the government's strategy will cover no more than 8% of newly infected persons, i.e. a few hundred confirmed clinical cases, no more. So what is the point of increasing the testing capacity, which has been so much undersized so far, to 700,000 tests per week? And a subsidiary question : **how do we find the 92% of unidentified cases?**

We propose a testing strategy, combining virologic AND serologic tests, to identify most healthy carriers in a given territory.

Reminders: virologic tests (PCR) aim to identify and isolate virus carriers in order to **break** the chains of transmission (**downstream** strategy: stop the spread of the virus downstream of the chains of transmission). Conversely, serologic tests aim to **reconstruct** the history of the epidemic by **tracing** the chains of transmission (**upstream** strategy: reconstructing the tree of transmission chains).

Let's first evaluate the number of virus carriers in an middle-sized city on May 11th. It has been estimated that there will be about 500 new cases of infection per day in Ile-de-France on 11 May ([Salje et al.](#) Figure S5-H3). This is for 10 million inhabitants. To fix the ideas, we consider a city of 50,000 inhabitants. We deduce that there will be 2 to 3 new cases of infection per day. The number of infected subjects can be estimated from this number of new cases of infection per day: during lockdown the number of infected subjects is about ten times greater since the transmission parameter β is equal to 0.1 per day ([Salje et al.](#)). There are thus about **25 virus carriers for an average town of 50,000 inhabitants.**

The challenge is therefore to find a few dozen healthy carriers (asymptomatic or paucisymptomatic) among 50,000 people ; and a number of clinical cases thus not exceeding a few units. To find the healthy carriers, we propose to test (with a virologic test and a serologic test) all the contacts of these confirmed cases, then all the contacts of these contacts tested covid+ etc. The idea is to try to reconstruct the transmission chains prior to the implementation of containment measures : since the beginning of containment, the branches of the contamination tree are no longer branched, and most of them have stopped growing. The objective is to **go up the transmission chains** to find the first virus spreaders and then go down their transmission chains to the terminal branches which are the current virus carriers, most of them being healthy carriers.

Let us then evaluate the number of tests to be carried out. We start with confirmed cases (either by a virologic or serologic test). Then, for each of these individuals, we look for its contacts during the two weeks preceding the first symptoms (not just the two days preceding the first symptoms, which would only provide the people he has potentially contaminated during his pre-symptomatic phase), which allows us to trace back to the previously infected contacts (notably the contact who contaminated the confirmed case we started from).

There are approximately 25 contacts in total to search for each confirmed case. In addition, there are approximately 20 confirmed cases per 50,000 population in the three weeks prior to May 11. Therefore, $20 \times 25 = 500$ tests per confirmed case should be performed first. Among the 25 contacts tested in a territory where the proportion of covid+ is p (p is of the order of 10 to 15% in the most affected regions and about 2% in the least affected regions) there will be an average of $25p$ covid+. In a heavily affected region there will therefore be an average of about 3 covid+ contacts. For these 3 covid+ contacts, the search procedure is repeated and 3×25 tests are carried out, of which a fraction p will in turn be tested covid+, providing about 9 covid+. If all these covid+ are different at the end of the second iteration, we will have found $20(1 + 3 + 9) = 260$ covid+ persons. Of note we know that each confirmed case corresponds on average to 12 other unconfirmed covid+ (since 1 case out of 13 represents 8%). This is exactly what is provided by the two iterations described above. And to carry out these two iterations it is necessary to perform $25(1 + 3 + 9) = 25 \times 13 = 325$ tests per confirmed case. This means that a total of about 6,000 tests have to be performed for an average town of 50,000 inhabitants.

Interestingly Koreans performed 25 times as many tests as there were infected subjects in Korea and thus were able to identify all infected subjects. Of note there were, as in Ile-de-France, 10 to 15% of contaminated subjects among the members of the Shincheonji sect, which was the main cluster of contamination.

In a **downstream strategy**, designed to break the active chains of contamination, the testing and isolation campaign must be sized up. We have seen that there would be no more than 2 to 3 new cases of infection per day, of which only 8% of apparent cases, hence 1 to 2 clinical cases per week would be observed. To recover all the associated cases (asymptomatic and paucisymptomatic) we will therefore have to carry out about **500 tests per week** using the iterative procedure described above.

In an **upstream strategy**, designed to go up the transmission chains to find the first virus spreaders and then go down their chains of transmission to identify all current virus carriers, we must find a few dozen healthy carriers. An iterative procedure has been proposed for this purpose, starting with the 20 or so confirmed cases found in the three weeks preceding 11 May. The number of tests (both serologic and virologic) has been estimated at 5,000. This number is largely overestimated because many contacts will be found in duplicate (or often more) during the procedure. Moreover, if each of the 20 confirmed cases were to provide the 12 previously estimated healthy carriers, about 250 virus carriers would be found, i.e. 10 times more than the 25 previously estimated healthy carriers. There is therefore a large margin, a priori guaranteeing the success of the screening campaign. Anyway the order of magnitude is clearly **a few thousand tests**. Moreover GIS (geographic information system) could provide significant help in identifying clusters and subsequent testing of all their members, thus accelerating the search for healthy carriers.

Finally, let's evaluate the feasibility of the testing campaign. Ile-de-France accounts for a quarter of all contaminations in France. With 700,000 tests per week, there will be 175,000 tests for the Ile-de-France region and therefore around 1,000 tests per week for an average city of 50,000 inhabitants. We can therefore hope to complete the testing campaign in a few weeks and thus be able to eradicate the epidemic from the city.

References

Mizumoto et al, Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020;25(10):pii=2000180. <https://doi.org/10.2807/1560-7917.ES.2020.25.10.2000180>

Salje et al, Estimating the burden of SARS-CoV-2 in France. 2020. pasteur-02548181

Annex

Estimation of the fraction of cases that are eventually confirmed :

- First calculation: Only 15% of symptomatic cases warrant hospitalization. As half of the cases are asymptomatic ([Mizumoto et al](#)), these 15% represent barely 8% of all virus carriers. And it is only these 8% that are actually tested positive (known as "confirmed cases").
- Second calculation: The average number of confirmed cases per day in France during the week of 21-28 April is 1280 and the number of subjects who were infected on 13 April, 11 days earlier (average time between infection and first symptoms) is estimated at 15,000 ([Salje et al](#). See Figure 3C). Thus, again, about 8% of the infected subjects were eventually identified.