

### First of all thank you for your insight into the zoonoses in our decryption last week!

In addition to my paper dated April 6<sup>th</sup>, a new study [1] was published on April 8<sup>th</sup> by researchers from the University of California veterinary school. By analyzing 142 cases of zoonotic disease outbreaks known since 2013, they found that rodents, primates and bats were identified as hosts of the majority of viruses transmitted to humans (75.8%) and domestic animals as carriers of 50% of the zoonoses identified! These results strongly emphasize the high share attributable to the destruction of biodiversity.

### What's been up on the Covid-19 disease battlefield since last week?

In French Guyana, the situation remains stable, fortunately there are no deaths. Of the 86 people infected on April 10<sup>th</sup>, 51 were cured, 9 remained hospitalized including 1 in intensive care. A cluster with 13 cases was declared in Cecilia, an Amerindian Arawak village near Matoury, in Cayenne area. The village was immediately quarantined by the authorities.

Globally, the outbreak is still worrisome, with more than 115,000 official deaths worldwide as of April 13. Fortunately, we are seeing the beginning of an epidemic plateau in Europe, a plateau very high in some of the countries most affected to date: Spain, Italy and France.

A recent American study revealed the results of its follow-up of 4 coronaviruses between 2010 and 2018 with hundreds of families in Michigan [2]. These coronaviruses are well known and have been circulating for decades, targeting young populations instead. The 4 coronaviruses showed a fairly marked seasonality, with epidemic growth in December, a peak in January-February, and a decline in spring.

We hope Covid-19 will behave the same way. However, this new virus remains very little known with significant contagiousness and a global geographic distribution which already affects 185 countries. It has spread to the southern hemisphere which is soon entering winter. We might therefore fear a reintroduction of this novel coronavirus in the northern hemisphere in the fall.



Marc Del Grande, Prefet of French Guyana (left) at the Pasteur Institute in Cayenne.

### Some countries are reflecting or starting deconfinement strategies. Would collective immunity be achievable in the short term?

As a strategy for preventing the epidemic and reducing its impact in terms of mortality, containment and barrier measures have been shown to be effective in protecting populations and avoiding congestion in hospital infrastructures. They slow the spread of the virus in the population.

***"A person automatically touches his face up to 3000 times a day!"***

The reverse side of the medal, is that they come at the expense of the collective immunity that some hope. This immunity would be possible once almost 60% of the population has been in contact with the virus.

However, recent field surveys in the most affected regions indicate that only 10-15% were in contact with the pathogen (confirmed by modeling carried out by Imperial College London). It is far too little at this point, and it indicates that we will have no other choice but to well anticipate the phase of **deconfinement to come: sufficiently progressive and organized** not to recreate the conditions of a new epidemic peak.

### What does a progressive and organized deconfinement exactly mean?

There are three areas to act on:

1. **Generalize the screening tests** [3] for the virus by PCR techniques (molecular research of the virus) while awaiting the development of serological tests (blood sample and search for antibodies against the virus), while associating it with a system digital tracking allowing targeted and rapid isolation of those affected
2. **Respect the barrier gestures:** massive use of masks and systematic hand washing. I remind that a person automatically touches his face up to 3000 times a day!
3. **Know and monitor the degree of contamination and protection of the population.** Serological testing is essential because it will detect in the blood: IgM and IgG antibodies, the latter providing long-term immunity.

*Clinical trials of a vaccine are divided into 3 phases:*

- *During phase I, small groups of people receive the test vaccine, to test the properties of a vaccine, its tolerability and laboratory parameters. Phase I studies mainly concern safety.*
- *During phase II, the clinical study targets a greater number of patients in the target population (age, state of health). We are seeking here to obtain preliminary information on the capacity of a vaccine to produce the desired effect (generally immunogenicity) in the target population and its general safety.*
- *During phase III, the vaccine is administered to thousands of people and tested for its efficacy and safety. The Phase III clinical trial is the pivotal study on which the decision to license or not is based and enough data must be obtained to demonstrate that the new product is safe and effective for the intended purpose.*

From the point of view of social organization, it will be necessary to go there in progressive stages, to continue isolating the people most at risk (elderly and/or with multiple pathologies) and to avoid excessive concentrations of people.

The search for treatments and vaccines is very active, and I encourage you to follow the multiple initiatives already launched to obtain a treatment in the medium term and a vaccine in the longer term.

***"We are witnessing an unprecedented dynamic in the search for vaccines!"***

### Can you provide us an insight on vaccine research in general?

The antiviral vaccines are traditionally divided into 2 large families:

- The **live attenuated vaccine**: it consists of living germs modified so that they lose their infectious power. These are very effective vaccines, used for example for measles, rubella, mumps.
  - The **inactivated virus vaccine**: the latter does not contain live infectious agents but may contain a fragment of an infectious agent, or all of an inactivated infectious agent. This family includes vaccines against influenza, polio, hepatitis B, whooping cough or rabies.
- For coronaviruses, as well as for HIV or hepatitis C, other strategies are being explored. **Recent advances in immunology and molecular biology have made it possible to considerably expand knowledge, and today we are exploring recombinant vaccine or messenger RNA vaccine.**

This vaccination strategy is essential, but it will rather target the medium-long term. Several steps are indeed necessary once the formula has been found: animal and then human test phases, validation of its safety, stability, then production, delivery, regional qualification. And the effectiveness of this vaccine will only be judged in the long term.

### What are your hopes for this novel coronavirus, keeping in mind that the previous epidemics of SARS (2002-2003) and MERS (2012) have not seen any vaccine entered the market. Do you have an explanation?

It should be remembered that we do not always end up with the development of a vaccine. We developed one for the H1N1 flu epidemic in 2009 (also known as swine flu), but no vaccine has indeed been deployed for SARS and MERS, two virulent coronaviruses.

This is due to several reasons, which are not found with this new coronavirus, including:

- the expected market for pharmaceutical laboratories, insufficient to allow the costly deepening of the development of subsequent phases.
- the SARS and MERS epidemics were, by comparison, quickly circumscribed. For MERS, human-to-human contagiousness was found to be low, and SARS had been contained due to drastic hygiene and quarantine measures.

To focus specifically on the **SARS-Cov-2, the exact name of the virus causing COVID-19 disease**, the Pasteur Institute is now expecting on a period of around 18 months, considering that WHO or European Medicines Agency experts expect similar timeframe.

However, we are witnessing an unprecedented dynamic in the search for vaccines! We had already mentioned the BCG booster vaccination (BCG being implemented for fighting against tuberculosis, see decryption IFGR no.1 of March 30<sup>th</sup>).

Around 50 vaccines [4] have been launched worldwide and vaccine candidates have even already entered clinical trials. I would like to highlight some of these initiatives.

The American biotechnology company Moderna Technologies is working on a **promising track**,

**although never developed before: the messenger RNA vaccine**, a molecule serving as an intermediary between DNA and the proteins it codes for. The clinical trial has just entered phase 1.

As it stands, this technique will target the protein S - spike, the main gateway of the virus into host cells, and which gives this particular form to the virus. The researchers hope that the expression of this protein will induce a protective immune response to the patient. Other companies around the world, in Asia, the United States and Europe (CureVac or BioNTech in Germany) are also working on similar leads.

**The Pasteur Institute is working on three research programs, including a recombinant vaccine from a strain of the attenuated measles virus.** By modifying its genetic heritage, it could present a protein from the coronavirus on its surface. This strategy has made it possible, for example, to develop a vaccine against chikungunya, which is now in phase III of development.

**Thank you Mirdad and see you next week!**

*Propos recueillis par Aziz Ouaabi*

### Recommendations and reading lists

[1] Study showing that the degradation of biodiversity is at the origin of the vast majority of zoonoses observed since 2013.

Global shifts in mammalian population trends reveal key predictors of virus spillover risk, Christine K Johnson & al. Apr. 8<sup>th</sup> 2020 - Proceedings of the Royal society. <https://doi.org/10.1098/rspb.2019.2736>

[2] Seasonality observed between 2010 and 2018 on 4 coronaviruses in Michigan (US).

Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan. Arnold S. Monto & al. University of Michigan. Published by Oxford University Press for the Infectious Diseases Society of America. 2020. <https://academic.oup.com/jid/article/doi/10.1093/infdis/jiaa161/5815743>

[3] Comparative analysis of the performance of sampling methods for diagnosis (nasopharyngeal sampling, sputum, bronchoalveolar lavage)

Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. Yang Yang & al. - Shenzhen laboratory of Pathogen and Immunity and Institut Pasteur of Shanghai. <https://www.medrxiv.org/content/10.1101/2020.02.11.20021493v2.full.pdf>

[4] Website listing the vaccines and treatments in development worldwide

<https://www.biocentury.com/article/304515>

[5] Progress of vaccines on the MERS (epidemic in the Middle East in 2012)

Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-Coronavirus. Chean Yeah Yond & al. Malaysia. <https://www.frontiersin.org/articles/10.3389/fmicb.2019.01781/full>

[6] Algorithm codeveloped by the Pasteur to guide via digital tools, people who think they have been exposed to the novel coronavirus (COVID-19 disease)

<https://maladiecoronavirus.fr/se-tester>

[7] Effects of temperature and humidity on the development of covid-19.

*Temperature, Humidity and Latitude Analysis to Predict Potential Spread and Seasonality for COVID-19.* [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3550308](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3550308)

[8] The possible origins of covid-19, Nature article of March 26, 2010

*Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins.* [https://www.nature.com/articles/s41586-020-2169-0\\_reference.pdf](https://www.nature.com/articles/s41586-020-2169-0_reference.pdf)