SARS-CoV-2, "common cold" coronaviruses' cross-reactivity and "herd immunity": The razor of Ockham (1285-1347)?

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Non sunt multiplicanda entia sine necessitate

After the rapid spread of coronavirus-19 infectious disease (COVID-19) worldwide between February and April 2020, with a total of 5,267,419 confirmed cases and 341,155 deaths as of May 25, 2020,[1] in the last weeks we are observing a decrease in new infections in European countries, and the confirmed cases are not as severe as in the past, so much so that the number of patients transferred to intensive care for the worsening of the systemic and pulmonary disease is dramatically decreasing.

In Italy, the lockdown of social and work activities begun on March 10th, 2020; following a decrease of new confirmed COVID cases, on May 4th there was a partial opening of these activities without any impact on the trend on new confirmed cases. Indeed, the epidemic curve has been constantly bending from 6,557 on 21st May to 300 new cases on 25th May. Furthermore, currently most of admitted COVID-19 cases appear paucisymptomatic or mild to moderate infections, and the number of COVID-19 patients in intensive care is stably decreasing.[2]

At the beginning of the epidemic, the number of secondary infections (R_0) produced by a COVID-19 case in a population where everyone is susceptible ranged from 2 to 2.5.[3] By using the formula 1- ($1/R_0$) was possible to estimate that the minimum ('critical') level of population immunity, acquired via vaccination or naturally-induced (*i.e.* after recovery from COVID-19), to halt the spread of infection in that population should be around 60%.

Where are we now? According with the literature,[4] acute antibody responses to SARS-CoV-2 occur in almost all patients with COVID-19, even though the neutralising activity of these antibodies is under investigation. The seroprevalence surveys in Europe are ongoing, with limited data. In Lombardy region in Italy, that was the center of a dramatic cluster of COVID-19 infections, a seroprevalence survey on about 66,000 persons, healthcare workers and citizens on quarantine, evidenced a seroprevalence of 13.6%;[5] however, lower seroprevalence, *i.e.* less than 5%, are estimated in south of Italy (personal data). Therefore, the herd immunity still seems very far away.

What is clear, is the progressive decrease in the incidence of new COVID-19 cases after the implementation of lockdown strategies in different countries, especially in Europe. What is less clear, is the persistence of this decrease, albeit slower, after the "opening" of social and work activities, as occurred in Italy, in spite of more opportunities for sharing SARS-CoV-2 infection following the loosening of lockdown measures. Furthermore, this decrease is not affected by the daily number of nasopharyngeal swabs, that are indeed increased in the last weeks. Moreover, the number of severe cases requiring intensive care is decreasing with less bed occupied in intensive care by COVID-19 patients.[2] Of note, during the dramatic increase of COVID cases, the need for intensive care beds pushed the regional health authorities to open new intensive care facilities.

What causes this change of course of the epidemic? Epidemics typically have a rapid increase, a peak with a stationary phase and a decrease that depends on the R_0 reduction or the attainment of a herd immunity. Then the epidemic shuts down.

A possible explanation of the decrease of new confirmed and of less severe COVID-19 cases could be the effect of the lockdown that reduced the occurrence of at risk contacts, *i.e.* less COVID-19 cases and less severe ones (older people are more prone to be compliant to lockdown measures). However, this does not totally explain why an increase of cases did not occur after the loosening of restrictive measures.

Another likely explanation is the effect of environmental factors, *i.e.* humidity, temperature and Ultra Violet (UV) on SARS-CoV-2. The role of environmental factors on COVID-19 spread is actually controversial. Recently, two studies have led to different conclusions: higher temperature, pressure, and UV may be associated with less COVID-19 prevalence and humid climates and summer weather will not substantially limit pandemic growth.[6,7] However, there is no evidence that higher temperatures may modify virulence and pathogeniciy of SARS-CoV-2.

More recently, a new insight in the immune response to coronaviruses has led to the detection of SARS-CoV-2-reactive CD4+ T cells in ~40-60% of individuals that were unexposed to SARS-CoV-2, suggesting cross-reactive T cell recognition between circulating 'common cold' coronaviruses, *i.e.* HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E, to varying degrees and SARS-CoV-2.[8] Six different unexposed donors with IgG against "common cold" coronaviruses had indeed SARS-CoV-2-reactive CD4+ T cells, demonstrating that the cross-reactivity is relatively widely distributed.[8] Virologists are claiming that there is no evidence of SARS-CoV-2 mutations causing less virulence and change of pathogenicity,[9] therefore, bending the epidemic curve could be simply the effect of progressive exhaustion of people susceptible to infection either due to a COVID-19 infection or for previous/recent "common cold" coronaviruses' infections.

We have no certainty on how SARS-CoV-2 pandemic will evolve in the coming months. However, instead of concentrating most of the efforts on "unlikely" therapies, such as the case of hydroxychloroquine,[10] it would be better to know how the immune response to this virus develops and how previous exposures to "old" coronavirus can influence the immunity of the population against SARS-CoV-2.

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