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Communications

On the intrinsic nature of viral pathogenesis: The assumption of a Darwinian paradigm to describe COVID-19 pandemic

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ABSTRACT

Our hypothesis about evolution of the COVID-19 pandemic foresees an inverse relation between infectivity (R0) and lethality (L) of SARS-CoV-2. The above parameters are driven by a continuing mutation process granting the virus a clear survival advantage over virulence. For interpreting this relation we adopted a simple equation, $R0 \times L \approx k$, by which R0 and L depend upon a constant k, that corresponds to an intrinsic property of the viral species involved. The hypothesis was verified by following changes of the R0 and L terms of the formula in the different variants of SARS-CoV-2 that progressively appeared. A further validation came when the equation was applied to pandemic and epidemic influenza type A viruses, Ebola virus and measles virus. We believe this equation that considers virus biology in Darwinian terms could be extremely useful to better face infectious viral threats and validate virus-host molecular interactions relevant to viral pathogenesis.

Viruses, the predominant living entities dwelling the biosphere, necessarily depend on the hosts they infect, i.e. animal or vegetal cells, worms, simple and complex microorganisms, in order to self-reproduce in the form of their nucleic acid [1,2]. This obligate parasitism relies upon some virus-host interactions that are specific for each virus and could be traced back to three main biological parameters: i) infectivity/contagiousness, meant as the capability to spread from one host to the other; ii) virulence, as the degree of pathogenic insult or disease produced; iii) immune-evasion, as the virus ability to circumvent the host innate and adaptive antiviral response. Infectivity and virulence of viruses that infect humans can be indisputably measured by taking into account two basic quantifiable parameters that are linked to viral pathogenesis, i.e. the virus basic reproduction number (R0) during the exponential phase of the outbreak and the virus-induced lethality (L), respectively [3,4]. Immune-evasion, instead, is particularly difficult to define, due to the variability, complexity and large pleiomorphism of the viral and human genes involved that make virus escape from the host defense a singularity more than a directly quantifiable phenomenon [5]. However, for the sake of simplicity, immune-evasion (IE) can be recapitulated in the infectivity parameter for being viewed as an acquired genetic trait generally ascribable to the reproduction potential of the virus to which IE is clearly linked. Given these concepts, we want to prove here that the fate of SARS-CoV-2 pandemic can be reconciled in Darwinian terms with a selective advantage of the coronavirus that drives its evolutionary programme towards an increased contagiousness at the expense of virulence to guarantee persistence within the natural host. We used a mathematical equation that proves that a direct correlation exists between R0 and L that depends from a constant value k from which each either variable can be deduced in the course of the pandemic. The same concept holds true also for the spreading of other pandemic/epidemic viruses e.g. the influenzavirus, Ebola virus and measles virus that were used as a control. For the conceptual validation of our equation, when applied to SARS-CoV-2, we have herewith considered only the main variants of the coronavirus that develop in the course of the pandemic and not the innumerous distinct subvariants and quasi-species that are evolutionally accruing without becoming epidemiologically dominant and clinically relevant. Calculating k for any emerging virus responsible for a pandemic/epidemic could help to predict its biological behavior and to anticipate the consequences of viral infection at the public and global health levels.

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The herewith presented hypothesis factually rests on one of the first description interpreting microbiological evolution in response to an environmental agent, namely the Luria-Delbrück experiment of 1943, also called the "fluctuation test" [6]. This is, to our knowledge, the first biological experiment dealing with infectious agents to be deciphered with a mathematical formula. The test showed that genetic mutations coding for resistance to bacteriophages, rather than being a response to virus exposure, arise randomly in bacteria in the absence of selective pressure. In other terms, mutations are not induced by the environment, consisting of a newly introduced biological entity, but are rather pre-existing and naturally selected by the environment itself [6]. According to the chaos theory [7], mutations follow a "strange attractor" called the basin of attraction where those peculiar random mutations dynamically converge that are "driven" over time towards the best possible choice. A key feature to consider in the Luria-Delbrück experiment is the time factor. The longer is the time of exposure, the greater becomes the bacterial resistance to bacteriophages.[6] This time factor also holds true for COVID-19, a pandemic disease caused by the new coronavirus, SARS-CoV-2. It is in fact an accepted knowledge that the longer SARS-CoV-2 circulate in the population worldwide the more the virus replicates accumulating random mutations [8,9]. This phenomenon is generally believed to originate following a persistent/chronic viral infection of immunosuppressed subjects [9–14], a condition that would favor an unrestrained replication of the virus that thus accumulates a large number of new mutations. Although a great proportion of them may be lethal mutations, some are certainly advantageous for SARS-CoV-2 in terms of fitness. The "attractor" would therefore consist of a higher infectivity potential, as exemplified by the increasing R0 values of the different mutant strains establishing new variants (from Alfa to Omicron) and subvariants thereof. These variants, in turn, become prone to further evolution in the course of the pandemic. Thus, it cannot be disputed that Darwin's theory of natural selection acting through random mutations applies to viruses as well. The original Luria-Delbrück mathematical equation was formulated on the assumption that the mutation rate and the growth rate were constant but one can easily generalized them to ease these constraints. Could it then be hypothesized that evolution of the different variants of SARS-CoV-2 also follows a very specific law? Is there a mathematical formula that applies also to human viruses? It can be noticed that infectivity (transmission from one host to another) is greater going from Alpha to Omicron while lethality has an opposite development, highest in Alpha and lowest in Omicron [15,16]. If this holds true, the coronavirus has achieved its purpose, namely to be able to survive as a parasite for as long as possible while being able to infect the highest number of people, causing the least number of deaths.

Taking into consideration values from different repositories, SARS-CoV-2 R0 and L appears to be inversely proportional leading to the simple formula:

$$k \approx R0xL$$

As asymptomatic infections are relevant in the case of SARS-CoV-2 [17] and expected to lower the lethality rate, the L values can be corrected as follows.

$$Lc = [Lx(1 - \frac{\%A}{100})]$$

where Lc is the corrected L and %A is the percentage of asymptomatic subjects. If we assume that the number of asymptomatic infected people were roughly equal to 27 % in 2020 and 30 % in 2021 and now approximately equal to 40 % thanks to vaccines [18], the k product is almost constant and around 5, as estimated (Table 1).

Table 1
Calculated k for SARS-CoV-2 variants. R0 and L values were retrieved from the John Hopkins Coronavirus Resource Center, accessed in July 2022 [18]. A% stands for percentage of asymptomatic patients.

SARS-COV-2	R0	L%	A%	k
B1.1.7 (Alfa)	4	2	27	5.84
B.1.351 (Beta)	4.5	1.8	27	5.91
P.1 (Gamma)	5	1.6	30	5.60
B.1.617 (Delta)	7	1.1	30	5.39
B.1.1.529 (Omicron)	14	0.6	40	5.04

The fact that the first well described SARS-CoV-2 variant, Alfa, had a constant k = 5.84 and that this value remained almost stable all subsequent variants over time, would drive to a notion suggesting that the process of virus evolution over time responds to an intrinsic pre-determined biological feature of this virus. This may accompany SARS-CoV-2 until the coronavirus hopefully becomes endemic. On the other hand, with the exception of the beta variant (Table 1), the k constant tends to decrease over time, although remaining in the same order of magnitude and close to the initial value.

A confirmation that our hypothesis has a rationale comes from the application of our formula: $k \approx R0 \times L$ to the H1N1 subtypes of influenza type A virus, both the pandemic and the seasonal strains. Despite the fact that R0 and L available for SARS-CoV-2 are actual numbers, while influenza data are calculated estimates [19], we obtain a k value that fluctuates around 0.25, with the exception of the Spanish influenza for which R0 and L parameters are difficult to define (Table 2).

Interestingly, these values, considering all type A viruses, are admittedly lower than those of SARS-CoV-2 [3], suggesting that k could represent an intrinsically virus-specific feature. A proof of the concept of this conclusion comes when the influenza k value is substituted in the equation for the k obtained for SARS-CoV-2. In this case, we would obtain an R0 equal to 50, a value that has not been reached by any known human virus and that is almost threefold higher than the R0 of the most contagious so far Omicron BA.5 subvariant.

Furthermore, the much lower k value of influenza virus with respect to the one obtained for SARS-CoV-2 would mathematically confirm that COVID-19 is a more serious disease than flu by approximately twentyfold, on average.

To further prove these conclusions, we took advantage of the 2014 Ebola virus outbreak, in West Africa the largest epidemic of the genus Ebolavirus to date. This outbreak began in Guinea in December 2013, spreading to Sierra Leone, Liberia and Nigeria. Such an epidemic gave us the opportunity to apply the formula to a virus circulating in different geographical regions with diversities in the reported R0 and L. As shown in Table 3, k values are almost constant and represent very high estimates linked to the danger and mortality of the Ebola virus. This, in turn, would confirm that k is an intrinsic feature of the virus, nicely correlating with its dangerousness and aggressiveness.

Table 2
Calculated k for Influenza type A virus parameters. Values adopted for k calculation are calculated estimates [19].

Influenza type A virus	R0	L%	k
Spanish H1N1 – 1918	2	0.1–1	0.2–2
Asian H2N2 – 1957	2	0.15	0.3
Hong Kong H3N2 – 1968	1.9	0.15	0.29
Swine H1N1 – 2009	1.6	0.14	0.22
Seasonal H1N1/H3N2	2.1	0.1	0.21

Table 3
Calculated k for 2014 Ebola virus parameters. Values adopted for k calculation are reported in [20].

Ebola virus	R0	L%	k
Guinea	1.51	74	111
Sierra Leone	2.53	48	120
Liberia	1.59	71	112

Table 4
Calculated k for measles virus parameters. Values adopted for k calculation are reported in [21,22].

Measles virus	R0	L%	k
1980	14	3	42
1990	18	2.5	45
2000	16	2	32
2005	14	1.5	21
2014	12	1	12

Finally, as depicted in Table 4, by applying the formula to the measles virus for which R0 and L are known over time, k values remain almost constant from year 1980 to year 1990, after vaccine introduction. Interestingly, while remaining in the same order of magnitude, k values for measles virus decrease from 42 to 12 over the period of observation (30 years). Such a finding, on one hand, supports k as an informative virus specific feature, on the other hand, suggests that k like L values tend to vary, and specifically to decrease. This phenomenon would depend on several other factors in addition to virus adaptation to the host i.e.the time-length of virus circulation among humans with acquisition of natural or artificial immunity by the population as well as improvements in cares and specific treatments.

In conclusion, for the viruses we have considered in this report, namely SARS-CoV-2 variants, influenza type A subtypes, Ebola virus and measles virus, the product of R0 and L gives an almost constant value. Fatality rate and infectivity follow a pattern supporting the formula.

$$k \approx R0xL$$

according to the general principle that a high R0 value relates to a low L value and vice versa. Since k seems to nicely correlate with the seriousness of disease, its knowledge could be useful for an effective management of emerging infections: the higher is the value of the constant the more fatal is the virus. Furthermore, the fact that k lowers over-time (Table 1 and Table 4) depending on virus and host-specific factors can represent an even more informative parameter for Public Health evaluations.

Obviously, the hypothesis of a constant relationship between virulence (measured as L) and infectivity/contagiousness (measured as R0) in different virus species causing acute infections has to be further confirmed by properly designed longitudinal field investigations since a review of replication and fatality rates during the last 50 years is not easily inferred from published studies. We reckon that our simple formulation, if thoroughly validated, could greatly help public health systems to deal with medical and epidemiological problems linked to the emergence/re-emergence of infectious viral threats. It may also inspire new ways of looking at virus-host molecular interactions and quantifying their respective impact on some relevant pathogenic manifestations.

1. Authors' contributions

GP conceived the hypothesis and developed it with input from PR and AC; GP wrote the original draft with review and comments from PR and AC.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. No funds were used for this work.

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