"Accidents waiting to happen" – insights from a simple model on the emergence of infectious agents in new hosts.

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Abstract

This study evaluates through modeling the possible individual and combined effect of three populational parameters of pathogens (reproduction rate; rate of novelty emergence; and propagule size) on the colonization of new host species – putatively the most fundamental process leading to the emergence of new infectious diseases. The results are analyzed under the theoretical framework of the Stockholm Paradigm using IBM simulations to better understand the evolutionary dynamics of the pathogen population and the possible role of Ecological Fitting. The simulations suggest that all three parameters positively influence the success of colonization of new hosts by a novel parasite population but contrary to the prevailing belief, the rate of novelty emergence (e.g. mutations) is the least important factor. Maximization of all parameters result in a synergetic facilitation of the colonization and emulates the expected scenario for pathogenic microorganisms. The simulations also provide theoretical support for the retention of the capacity of fast-evolving lineages to retro-colonize their previous host species/lineage by ecological fitting. Capacity is, thus, much larger than we can anticipate. Hence, the results support the empirical observations that opportunity of encounter (i.e. the breakdown in mechanisms for ecological isolation) is an fundamental determinant to the emergence of new associations - in special of Emergent Infectious Diseases - and the dynamics of host exploration, as observed in SARS-CoV-2. Insights on the dynamics of Emergent Infectious Diseases derived from the simulations and from the Stockholm Paradigm are discussed.

"Accidents waiting to happen" – insights from a simple model on the emergence of infectious agents in new hosts.

Running Title: A simple model for the success of emergence of infectious pathogens

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Summary: This study evaluates through modeling the possible individual and combined effect of three populational parameters of pathogens (reproduction rate; rate of novelty emergence; and propagule size) on the colonization of new host species – putatively the most fundamental process leading to the emergence of new infectious diseases. The results are analyzed under the theoretical framework of the Stockholm Paradigm using IBM simulations to better understand the evolutionary dynamics of the pathogen population and the possible role of Ecological Fitting. The simulations suggest that all three parameters positively influence the success of colonization of new hosts by a novel parasite population but contrary to the prevailing belief, the rate of novelty emergence (e.g. mutations) is the least important factor. Maximization of all parameters

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Keywords: Individual-based model, host-switching, emerging infectious diseases, Stockholm Paradigm.

Introduction

Understanding the ecological mechanisms influencing the origin and evolution of host-pathogen associations is fundamental and it became a vigorous area of research in human health, agriculture, and food security, during recent years (Heard and Hauser, 1995; Woolhouse et al., 2005; Brooks et al., 2014). These studies are of special interest, considering the so-called crisis of Emerging Infectious Diseases (EIDs), present and future (Brooks et al., 2019). This crisis is the fulfilling of the prediction that EIDs are "accidents waiting to happen" (Brooks and Ferrao, 2005).

However, such studies are strongly influences by the researcher's perspective of its accepted theoretical evolutionary framework (see a summary of this under a historical perspective in Nylin et al. 2018; Brooks and Boeger 2019; Brooks et al. 2019; Agosta and Brooks 2020), often influenced by the perspective that parasites are ultimate specialists (Agosta et al., 2010). Traditionally, the nature of host-parasite/pathogen associations is regarded as a symmetrically selective interaction built under a 1:1 relation in a context of strong selective pressures (Kaltz and Shykoff, 1998). This vision generated a paradox - the Parasite Paradox (Agosta et al., 2010). The Parasite Paradox results from the accumulation of studies on host-parasite evolution in the last 40 years that, even utilizing protocols strongly biased towards co-speciation, still detected a large amount of what has been called to this date as host-switching (Krasnov and Shenbrot 2002; Hoberg and Brooks 2008; Agosta et al. 2010; De Vienne et al. 2013). Increasing phylogenetic and historical evidence points out that expansion in host range (=host repertoire according to Braga et al. 2018) is a primary dynamic in pathogen evolution and ecology. The complex structure of host-pathogen associations strongly sustain that the widely held evolutionary paradigm, which has been conceptually dominant for a century, cannot accommodate the present knowledge on the origin and evolution of symbiotic associations (Nylin et al., 2018).

The Stockholm Paradigm (Hoberg and Brooks, 2015; Brooks et al., 2019) provides such a theoretical framework. The fundamental element of this new perspective on the evolution and ecology of associations is the recognition that the vast majority of ecological changes occur through Ecological Fitting (Janzen, 1985a; Agosta and Klemens, 2008). The other two elements of the Paradigm - the Oscillation Hypothesis (Janz and Nylin, 2008) and the Taxon Pulse (Erwin, 1985) - are thought to represent emergent properties of the complex system composed of species that interact – with other species or the environment - under the ability to change by Ecological Fitting (Janzen, 1985; Brooks et al., 2006; Agosta and Klemens, 2008; Brooks et al., 2019).

Under the framework of the Stockholm Paradigm, Araujo et al. (2015) developed a mathematical model that evaluated the colonization of new host species by an evolving population. The simulations support the postulate that host colonization by Ecological Fitting is likely ubiquitous. Among other conclusions, Araujo et al. (2015) also suggested that successful colonizations are not limited to a high degree of compatibility of the pathogen population to the new host. Support for this perspective has been recently revealed by empirical experimentation (Khokhlova et al., 2020). Araujo et al. (2015) also indicate that poorly adapted pathogens can survive in a new host despite being in a sub-optimum condition, whereas they did not explicitly explore populational parameters that might influence the pathogen's colonization success.

The Stockholm Paradigm was recently expanded to incorporate any process of ecological change in evolution (Agosta and Brooks, 2020), including invasive species (Hoberg, 2010), phytophagous insects (Agosta, 2006; Nylin et al., 2018), ecological associations and community structuring (Wilkinson, 2004), and plant–bird pollination (Janeček et al., 2020). Colonization of new conditions, reflecting change from the ancestral selective pressure, most likely occur by ecological fitting in association to environmental and ecological disruptions (Brooks et al., 2019) and far less frequently by immediately preceding releasing mutations (see also Morse 2001).

Hence, in the present work we expand the study of Araujo et al. (2015) using simulations based on an individual-based model (IBM) considering elements of the Stockholm Paradigm to explore the significance and interaction of selected parameters that could be considered important for the success of colonization of new host species. The model is focused in host-pathogens systems, as Araujo t al. (2015). Although methodologically different, it can be applied to equivalent ecological changes, such as similar studies that developed other type of models to study, for instance, invasive species (e.g. Pkalski 2003). The tested parameters are the reproduction rate, the rate of novelty emergence (analogous to mutation rate), and the propagule size of the founder pathogen population, all of which are frequently considered as key population parameters in studies of biological invasion and epidemiology (Woolhouse, 2001; Dobson, 2004; Lockwood et al., 2005; Woolhouse et al., 2005; Braendle and Flatt, 2006; Hoberg, 2010; Hurford et al., 2010; Briski et al., 2012; Johnson et al., 2015; Mason, 2016; Gould and Stinchcombe, 2017).

The resulting simulations strongly support previous accounts on the process of colonization of new environmental conditions - in this case of new host-pathogens associations under an ecological perspective - and provides new insights into the process of emerging infectious diseases. The overall result of the simulations provides instrumental support to the recognized crisis of emergence of new infectious diseases (Fauci, 2001; Morens et al., 2004; Brooks and Ferrao, 2005; Brooks et al., 2014; Hoberg and Brooks, 2015; Mondragon et al., 2018; Morand and Figuié, 2018).

The model

An individual-based model (IBM) was designed to investigate the influence of some populational parameters on the colonization success of a new host species. During simulations, pathogens with variable propagule sizes, reproduction rates, and rates of emergence of phenotypic novelties were challenged by new host species representing different levels of compatibility (which are related to the selection pressure that the new host represents). The consumer-resource system can be applied to several different types of symbioses and ecological associations; for simplicity, hereafter we will designate these as the host-pathogen interaction. The model (written in Fortran) is available through Github (https://github.com/sofiagalvao2020/SimpleHost_-switching).

Pathogen and host descriptions:

Each pathogen i is described by a compound phenotype (=*fundamental capacity space* as defined in Agosta and Brooks 2020) of G binary individual phenotypes. The binary phenotypes can assume the values of either one or zero, which can be understood as the expression of two distinct traits within the same locus or set of loci. The sum of all characters defines the individual's compound phenotype (=*realized capacity space* of Agosta and Brooks 2020), which can vary between 0 and G. This *capacity space* is composed by inheritable features, subjected to change over generations, and under selection according to its compatibility to the host. The compound phenotype is labeled as $p_{i,n}$, in which the subscripts identify the pathogen i of the generation n . For the beginning of the simulation, the sum of all "loci" is identical for all propagule individuals- creating a standard populational compound phenotype p_0 at the start of the colonization attempt.

For simplicity, as in Araujo et al. (2015), the host is characterized by a single number (p_h) which represents the optimum value of the compound phenotype imposed on pathogens. It is a fixed throughout the simulation.

Here we assume p_h = G/2. Besides defining an interaction pressure around this optimum value, the host is also represented by a carrying capacity on the pathogen population of K individuals.

Dynamics

The dynamics starts with a propagule size of N_0pathogen individuals challenged to colonize the host - there is only one colonization attempt per simulation. For simplicity, their phenotypes are randomly defined, but when more than one pathogen individual is considered, they present identical compound phenotypes$p_{i,n=0}$ $=p_0$ [?] i – that is, they have the same fitness in the new host but carry different phenotypes (i.e. represent distinct *fundamental capacity space*). Each iteration step represents a generation n where the pathogens will undergo *Selection* and *Reproduction* (Fig 1), as detailed below.

Selection

The selection is imposed as the survival probability of each pathogen$i$ in a given generation n and it follows a normal distribution:

$P_{\text{survival}} = exp\left[\frac{-d^2{}_{i,n}}{2}\right]$, (1)

where

$d_{i,n} = \frac{p_{i,n} - \mathrm{p}_h}{\sigma}$ (2)

is the distance between the pathogen compound phenotype ($p_{i,n}$) and the optimum imposed by the host (p_h) in units of the deviation rate (σ). The deviation rate represents the selection strength imposed by the new host - the larger the deviation rate, the larger is the diversity of phenotypes that are capable of surviving on that specific host (Fig 1). For the propagule population - with all individuals presenting the same compound phenotype p_0 - the initial phenotype distance from the propagule to the host is$d_0 = (p_0 - p_h)/\ \sigma$. The model imposes this survival probability (Eq. 1) to every individual, and the survivors ($N_{s,n}$) go to the next model step, *Reproduction* .

Reproduction

At this step, the pathogens that survived the previous step (*Ns,n*) produce offspring depending on the reproduction rate (*b, the* average number of descendants per parental) and the carrying capacity (K). For simplicity, we assume asexual reproduction. The number of descendants for the next generation*n+1* will be $N_{s,n}$*b if this value does not exceed K , otherwise, the number of descendants is K . Random individuals of the surviving population are selected to generate one offspring with reposition - the progenitor can be selected more than once. This process is repeated until the total number of descendants is achieved. Each descendant inherits the same chain of characters of its progenitor with a probability μ of incorporating a novelty per locus (i.e. changing from 0 to 1 or from 1 to 0). After all reproduction events, the progenitors die and the descendants constitute the next generation that will be subjected to the new *Selection* and*Reproduction* cycle (Fig 1).

The rate novelty emergence (μ) refers to any kind of novelty introduced into the pool of capacity of the individual, indirectly influencing the pathogen's fitness to the host. These evolutionary novelties can emerge, accumulate, and be maintained throughout generations simulating inheritance mechanisms, comprising the*capacity space* of the pathogen (called *information space*in Brooks and Agosta 2012, Jablonka et al. 2014, Brooks et al. 2019; see also Agosta and Brooks 2020). We refrain from using "mutation rate" - as opposed to "rate of emergence of evolutionary novelty" - to avoid the strictly genetic meaning of the expression used in the Modern Synthesis (see Brooks and Agosta 2012; Laland et al. 2015; Agosta and Brooks 2020).

Simulations and data analyses

For each parameter combination, we ran 700 simulation repetitions for 1,000 generations or until the pathogen population went extinct. We then calculated the proportion of simulations without extinction and defined it as the *probability of successful establishment* . The sensibility of the probability of successful establishment to each parameter was calculated by varying two of them and fixing the remaining ones (the fixed values are highlighted in Table 1). The parameterp_0 was always one of the varied parameters and it varied between the fittest (p_0=p_h=$G/2$) to the least fit value (p_0 =G). Given that the propagule survival probability (Eq. 1) depends only on d_0 , we fixedσ = 10 and, as a consequence, the propagule compound phenotype distance from the host varied according to$0 \leq d_0 \leq G/20$. The investigated values of novelty rate (μ) are 0, 10^{-6},10^{-5}, 10^{-4}, 10^{-3}, 10^{-2},and 10^{-1}. Higher novelty values, such as 10^{-2} and 10^{-1} are considered analogs of the high mutation rates observed in viruses (e.g. Drake and Holland 1999). Furthermore, although biologically unreal, the null value forμ represents the inferior limit of our analysis. We also varied the reproduction rate (b), propagule size (N_0 ,), compound phenotype size (G), and carrying capacity (K) (Table 1). Our simulations were qualitatively invariable for the parameters G and K - only results in varying b , μ , N_0, andd_0 are presented.

Results

We simulated the success of establishment of the pathogen population during colonization of a new host and, when pertinent, the evolution of its compound phenotype under the new selective pressure. Parsing these components allowed a better understanding of the individual and combined influence of distinct rates of novelty emergence (μ), propagule size (N_0), and reproductive rate (b)_ on the success of establishment of a new association and the behavior of the fitness and size of the population of pathogen following colonization of a new host resource. All analyzed parameters were evaluated under variable distance of the propagule compound phenotype from the host (d_0) and revealed their influence on the probability of establishment of the pathogen population in the new host (Fig. 2). For a single propagule (N_0 =1), the increase of $d_0$gradually reduces the probability of establishment (Fig. 2a and b) – which was an expected result since the survival probability decays following this distance (black curves in Figs. 2 represent Eq. 1 for the propagule, $d_{i,n}$ =d_0). For the pathogen population to colonize the new host, it needs to survive successive selection events - therefore the probability of establishment is lower than the survival probability recovered for a single colonizing individual to persist until the first reproduction (the black curve in Figure 1).

Greater reproduction rates (b) favor the pathogen establishment (Fig. 2a). As b increases, the establishment success approaches the probability of one individual surviving the selective forces of the new host species (in Fig. 2a; compare non-black probability curves approaching the black curve as b increases). For high $b$rates (e.g. $b = 7.5$), the probability of establishment of the pathogen population will be the same as that expected for a single individual surviving until the first reproductive event of the simulation - and the probability of survival will depend only on the effect of d_0 .

Only high novelty rate values (10^{-2} and 10^{-1}) had a measurable effect on the populational probability of establishment - all other variations of novelty rate had practically the same low effect on the probability (Fig 2b). For novelty rates between 0.0 and 10^{-3}, the probability of success practically did not differ, reaching 0 for $d_0 \approx 1$ (propagule compound phenotype app. one standard deviation distant from the optimum imposed). The effect of the increasing novelty rate between these values is more evident on the population growth; the population reaches the carrying capacity about twice faster whenμ =10^{-4} than when μ =0 (Fig 3). Less than 10% of establishment success was detected for non-synergic simulations when $d_0 = 2$, despite the novelty rate (Fig. 2b).

Simulations have shown that a small increase in the propagule size (from 1 to 10) greatly expanded the diversity of compound phenotypes which resulted in a probability of success greater than 90% for pathogens with a d_0 <0.9 (Fig. 2c). For larger propagule sizes, this success extends up to$d_0 \approx 1.2$. The propagule-size

effect was significant for the survival rate of the compound phenotypes that do not meet the optimum imposed by the host, maximizing the survival rate of the neighboring phenotypes as the propagule size increases. This high probability effect quickly diminishes, depicting a cliff-like pattern for phenotypes survival probabilities higher than $d_0 \approx 1.2$, independent of the propagule size.

Finally, the simultaneous maximization of all parameters (B=7.5;μ =0.1; N_0 =200) resulted in a synergetic effect on the probability of success of colonization (Fig. 2). Under this scenario, even host lineages representing distant resources (resources that are less compatible with the pathogen requirements/capacity) have a high probability of colonization, far exceeding the probability observed for the populational parameters of the pathogens tested independently (Fig. 2).

As expected, based in every simulated scenario with a non-null μ , the emergence of phenotypic novelties in the generations following colonization allowed the compound phenotypes to evolve towards and stabilize around the optimal fitness value imposed by the host (Fig. 3). The greater the novelty rate (μ), the faster the evolution towards the optimum, also increasing the diversity of compound phenotypes (Fig. 3, μ $=10^{-2}$). During simulations, population size rapidly reaches the established carrying capacity. Even though higher values of μ favors population growth, the carrying capacity is achieved much earlier than phenotype stabilization for all scenarios (Fig. 3). Surprisingly, even in the absence of novelties (Fig. 3, μ=*0*) many simulated pathogen populations persisted and achieved the carrying capacity in the newly colonized host species.

Varying rates of the emergence of evolutionary novelties revealed also an unexpected outcome on the qualitative profile of the populations, following colonization. High rates of emergence resulted in the retention of compound phenotypes (variants) present in the initial and previous populations during populational growth, with correspondingly larger load (something analogous to the concept of genetic load; Wallace 1970) (Fig. 4a). Lower rates of novelty emergence resulted in populations that depict smaller phenotypic variability, with greater loss of pre-existing phenotypes (Fig. 4b). By maximizing every other parameter, the expansion of phenotypes is even larger, indicating that the increased maintenance of ancestral phenotypes is also influenced by other populational parameters besides μ .

Discussion

The general result of the simulations suggests that the increase in the rate of evolutionary novelty emergence, reproductive rate, and propagule size influence positively the success of colonization of new hosts by a novel pathogen population (Fig. 2). However, within the scope of the simulations, the different values of the explored parameters resulted in distinct impacts on this success. By far, the most significant impact was observed for the number of propagules; even not adapting to the selection of the new host, due to the complete absence of emergence of novelties imposed by the model, an initial population composed of 10 colonizers resulted in a significant increase of the probability to thrive and persist under suboptimal fitness, even in hosts representing relatively small compatibility ($d_0 \approx 1$).

Indeed, propagule pressure is extensively known to positively influence the colonization of new host species (May et al. 2001; Hatcher et al. 2012) - or geographic areas and corresponding communities in the case of invasive species (Sax et al. 2007; Lockwood et al. 2009; Cassey et al. 2018). Large propagule sizes are usually linked with the reduction of consequences of demographic (e.g. stochasticity and Allee effects) (Hufbauer et al. 2013) and genetic (founder's effect) (Simberloff 2009; Roman and Darling 2007) processes observed in small population size during changes in ecologic and geographic distribution. Since every simulation involving variation in propagule size used a low rate of emergence of evolutionary novelty and the relative fitness of propagules were kept unchanged (same d_0 despite qualitative differences in the combination of loci), the advantage conferred by increasing propagule sizes during colonization appears to be associated with demographic issues, most likely stochastic, as we did not model social collaborative processes nor limitation in the encounter of mates during reproduction (see Hufbauer et al. 2013). However, the rate of increase

in colonization success according to the imposed distance of the compound phenotype optimum of the new host diminishes with increasing values of the propagule size, not displaying a direct linear relationship (Fig. 2c).

Although less evident than the simulations with variable propagule size, increases in reproductive rate in less than 10 – fold (from 1.5 to 7.5) resulted in a more expressive increase in the probability of successful colonization than 1000-fold increases in the rate of emergence of novelties (from $\mu = 10^{-6}$ to$\mu = 10^{-3}$). This is an unexpected result, especially considering that the emergence of new associations - such as infectious diseases - is often linked by many to high mutation rates of the consumer associate (Pepin et al. 2008; Selman et al. 2012; Viana et al. 2015). Hence, our results indicate that the rate of emergence of evolutionary novelties alone (e.g. mutation rates for simple organisms such as viruses) has secondary importance in the colonization of new host species, as suggested in Araujo et al. (2015) and implicitly by the Stockholm Paradigm (Brooks and Hoberg 2007; Brooks and Boeger 2019; Brooks et al. 2019; Agosta and Brooks 2020). The accumulation of accessible historical information - termed the *information space*by Brooks and Agosta (2012) and Agosta and Brooks (2020) - is of greater importance for the events of host-repertoire expansion (i.e. the evolutionarily process that precedes what is known as host-switching; see Braga et al. 2018). It is the accumulation of heritable information by preceding generations (and ancestors) and its retention in the biological entities (i.e. populations, species) through time (=phylogenetic conservatism) that will determine the ability of lineages to endure ecological and environmental changes or to take advantage of opportunities (e.g. explore new resources, new habitats). Since compatibility (i.e. the distance to the actual host optimum) varies within individuals of a diverse pathogen population, regions of suboptimal fitness in the ancestral host - albeit potentially at low frequency in the population - may contain pathogen variants that are capable of reaching more distant (= more different) resources (new hosts) than originally higher-fitness variants (see also Araujo et al. 2015; Brooks et al. 2019). Consequently, under this scenario, actual rates of emergence of new inheritable evolutionary novelties (e.g. mutations) are less important than the number of individuals colonizing the new host (=propagule pressure), the rate of reproduction, and the degree of the variability in the original donor population.

When all three parameters considered are maximized, the simulations generate pronounced synergism (grey line in Fig. 2). The fact that this combination of values likely compares to those observed for viruses, particularly among RNA-viruses (Holmes 2009) is especially significant in understanding the evolution of this group of organisms and the corresponding emergence of infectious diseases. This outcome is compatible with the conclusions of Geoghegan, Duchêne, and Holmes (2017) that "cross-species transmission is a near universal feature of the viruses . . . , with virus-host co-divergence occurring less frequently. . . " For instance, continuous oscillations of host species were suggested as an intrinsically biological feature of coronaviruses (Menachery et al. 2017), but it is likely a property of viruses in general and perhaps of pathogenic bacteria as well. It is, thus, understandable that viruses and bacteria are the most common groups of organisms associated with emergent infectious diseases (Cleaveland et al. 2001; Woolhouse and Gaunt 2007; Gubler 2010; Pekala-Safińska 2018; Duarte-Neto 2019).

Since we expect that in the real-world representatives of the variants of pathogens are continuously exploring accessible resources (e.g. host species) (Brooks et al. 2019; Agosta and Brooks 2020) the emergence of new associations - or colonization of new environments - is expected when suitable matching (likely imperfect rather than perfect) between requirements of the pathogen, the resource (i.e. host properties), and/or environmental conditions meet. Therefore, the original host species represents an imperfect reference - but, perhaps, the only one accessible at this time - to describe the relative quality and the distance of the new resources to the pathogen. Phylogenetic distance between the host species involved in the host range expansion appears, within limits, to estimate the multidimensional space of traits that influence the compatibility of host and a specific pathogen lineage (Martiny et al. 2013; Braga et al. 2015; Streicker et al. 2010; Gilbert and Webb 2007). Since the resources defining compatibility vary according to both host and pathogen species, phylogenetic distances appear to be the only accessible proxy for the value ofd_0 , but it should be considered parsimoniously because evolutionary convergence of resources (Brooks and McLennan 2002) and the variability of the pathogen and hosts may influence also the outcome of the colonization

attempts (see for instance Boeger et al. 2005; Araujo et al. 2015).

The results of the present simulations are also fundamental to expand the understanding of the role of ecological fitting (Janzen 1985b; Agosta 2006; Agosta and Klemens 2008) on the evolution of ecological changes. As suggested previously by Araujo et al. (2015), newly established populations of pathogens may survive for many generations in a host even in the absence of adaptations. This is a more extreme scenario of what Darwin called the survival of the adequate (Agosta and Brooks 2020; Brooks and Agosta 2012). By surviving under these "suboptimal" conditions, pathogens may expand their temporal window for the "right" novelty to present itself and allow an increase in the population's fitness (adaptation) following the ecological change. For instance, Antia et al. (2003), modeling a scenario of colonization similar to the present simulations, suggested that early values of R_0 of a new pathogen may evolve towards an $R_0>1$ subsequently, under the selective pressure of the newly colonized host. However, after exploring the available Sloppy Fitness Space of the pathogen population (Agosta and Klemens 2008; Agosta et al. 2010; Brooks et al. 2019; Agosta and Brooks 2020), evolutionary novelties emerge randomly in the consumer species (the pathogen). Thus, the perfect match may never happen (i.e. a perfectly fit association) despite the influence of selection and the consumer may remain in a situation of continuous suboptimal fitness regarding its host species, a scenario analogous to that proposed by Sax et al. (2007) for invasive species.

Another additional perspective is that the newly established population of pathogens, although unchanged in its diversity due to the absence or limited emergence of novelties (phenotypic or genetic), may also expand the window of opportunity to encounter additional hosts representing more or simply adequate resources solely by inhabiting a host species with distinct ecological interactions with the surrounding environment. For instance, by depicting dissimilar behaviors, the adequate new host species may increase the probability of the new pathogen population to encounter other potential hosts not previously available (considering the ecology of the original host species) through a process that likely comprises one of the mechanisms of colonization of new hosts species. This is an empirically recognized process associated with many cases of emergence of new symbiotic associations - contemporary (Brown 2001) and historical (Braga et al. 2015) - including one of the possible pathways of SARS-CoV-2 to humans during the emergence (Ji et al. 2020; Zhang et al. 2020).

In the case of SARS-CoV-2, the scenario is even more worrisome since humans became one of the "stones" in the process of host-repertoire expansion by stepping stones (Braga et al. 2015; Brooks et al. 2019). COVID19 has rapidly expanded to almost every part of the planet, providing opportunities for the virus to colonize other human populations and animal species. Presently, pets – ferrets, cats, and dogs – and captive wild animals – such as minks, tigers, lions, macaques, Syrian hamsters, tree shrews, marmosets, and Egyptian fruit bats (Gryseels et al. 2020; Lin et al. 2020) are known empirically to be compatible hosts while a much greater range of host species has been suggested through modeling (Damas et al. 2020) - from old-world monkeys to anteaters. While many of the presently known compatible host species are not seriously affected by the virus, they certainly represent unique selective pressures and opportunities for broader dissemination through ecological fitting (as suggested above). Hence, we may anticipate influences connected with the acquisition of new host species on the genetic make-up of SARS-CoV-2 – among others, it may result in an increase in its overall genetic variability and/or on the emergence of unique haplotypes in isolated host populations (as suggested also by Franklin and Bevins 2020). Indeed, the nature of RNA-viruses replication influences by host and geographic expansion and isolation are already known to generate new variants (Franklin and Bevins 2020) with dissimilar potential virulence to humans. Such evolutionary changes may result in new strains of the viruses with the ability to generate diseases with symptomatic, virulence, and epidemiological characteristics distinct from the original strains (see Jerzak et al. 2007; Bordería, Stapleford, e Vignuzzi 2011). This epidemiological scenario is complicated by the accumulation of evidence suggesting that SARS-CoV-2 may take the opposite path (retro-colonizing humans), a situation already recorded among other coronaviruses for the Siberian musk deer *(Moschus moschiferus)* and ferrets (*Mustela lutreola*) (Hadfield et al., 2018; Van Der Hoek et al., 2004). Hence, despite the recognition that these retro-colonization events are likely rare (de Morais et al. 2020), they cannot be simply ignored in epidemiological surveillance systems. The significance of such scenarios and outcomes is further heightened

given the currently expected limited capacity for viruses to re-infect humans from domestic or synanthropic wildlife sources. Thus, potential pathways are not under active surveillance.

The simulations revealed yet another aspect of this host-exploration dynamics that makes the above-proposed scenario of retro-colonization of humans particularly important in health surveillance for EIDs. The simulations strongly suggest that at higher values of the rate of emergence of evolutionary novelties (e.g. mutation rates for viruses), the genetic profile of the pathogen - although changing qualitatively and quantitatively under the selective pressure of the new host resource - putatively retain "ancestral" variants at low frequency despite lower supposed fitness (Fig. 4B, C). This outcome provides theoretical support for the retention of the capacity of fast-evolving lineages to retro-colonize their previous host species/lineage by ecological fitting (Janz and Nylin 1998; Janz et al. 2001; Brooks et al. 2019). RNA viruses, such as SARS-CoV-2, are well known to evolve rapidly by mutation and hybridization (Holland et al. 1982), and the retention of variants may facilitate retro-colonizing of humans from recent spillover into other animal species. This perspective in phylogenetic conservatism analyzed along with available empirical data (such as that of Celorio-Mancera et al. 2016) and the real nature of novelty emergence (i.e. which includes more than just the idea that adaptation is solely associated with random mutations - Jablonka and Lamb 1995; Jablonka et al. 2014; Agosta and Brooks 2020) may provide a better understanding on the process of retro-colonization of the original host species/lineages. Hence, retro-colonization should be an important element in epidemiological monitoring (as suggested by Favoretto et al. 2019, Franklin e Bevins 2020, and González-Salazar, Stephens, e Sánchez-Cordero 2017), especially in cases of recent emergence and re-emergence of EIDs.

The combined results of this study provide further theoretical support for the assertion that "emerging infectious diseases are evolutionary accidents waiting to happen" (Brooks and Ferrao 2005). An increase in host-repertoire by pathogens, potentially associated with the emergence of a new infectious disease, is most likely to occur among closely related species of hosts, but it is also possible among distantly related hosts when the resource(s) is(are) convergent (see discussion on specilization in Brooks and McLennan 2002). **Capacity** is much larger than we can anticipate, and it is the **opportunity** of encounter (i.e. the breakdown in mechanisms for ecological isolation) that is a more essential determinant to the emergence of new associations (Araujo et al. 2015; Brooks et al. 2019; Agosta and Brooks 2020). And opportunities are more frequent during periods of environmental disruptions, many of which are associated with climatological fluctuations in the past (Hoberg and Klassen 2002; Brooks and Hoberg 2007; Hoberg and Brooks 2008, 2015; Hoberg et al. 2017). Climatological fluctuations usually change the permeability of pre-existing ecological barriers and promote shuffling in the composition of organismic communities, augmenting the rate of encounter of different host lineages, many of the same clade, fostering intense exchange in pathogens.

In general, climate oscillation and independent or accompanying environmental disruptions over evolutionary time have been a central determinant of opportunities for faunal mixing and pathogen exchange that have structured complex associations (Hoberg and Brooks, 2008). Climate and environmental disruption occur across scales and historically have had a substantial episodic behavior in the past (Hoberg et al. 2017). However, during what is now characterized as the Anthropocene, the outcomes of environmental disruption have become significantly more prevalent due to globalization, other human-associated actions, and also to climate change, which promote movements of wildlife, humans, and domestic species into new geographic range (Wilson 1995; Brooks and Boeger 2019). As a consequence, we expect EID's to become even more frequent in the years to come (Brooks et al. 2014). We have little control over capacity, but we can, to a certain level, monitor, avoid, and minimize the opportunity of encounter between parasites and compatible host species. This is the principle of the D.A.M.A. protocol (Brooks et al. 2014, 2019; Hoberg and Brooks 2015; Brooks and Boeger 2019).

However, even with an effective D.A.M.A. protocol established, the task to avoid the emergence of new diseases is especially difficult, considering available empirical information. Many of the most significant events in the history of life, and in the history of EID's, are likely the result of unpredictable incidents when compatible biological entities unexpectedly meet (opportunity). Attempts to generate new associations (hosts and pathogens, in this case) likely occur continuously, most being unsuccessful. However, a single successful

event may perpetuate the emerged association through evolution and have a significant influence on the future diversifications of the associates. That was likely the case for well-known symbioses, such as those of proto-eukaryotic cells and mitochondria, eukaryotic cells, and chloroplasts but also for many recent EIDs, such as HIV, Ebola, Dengue, Zika, Chikungunya, and, of course, Covid19.

Perhaps the final message from the empirical information accumulated from the recent emergence of infectious diseases and the dynamics revealed from the theoretical framework of the Stockholm Paradigm (Brooks et al. 2019) and associated evolutionary models (Araujo et al. 2015) is that we cannot "lower our guard". These events are evolutionarily dynamic processes, with pathogens incessantly exploring the space of compatible host species (Brooks et al. 2019). And we – and other domesticated species -are certainly one of the most abundant, available, ecologically diverse, and widespread species of potential host on this planet.

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Conflict of interest statement

The authors report no conflict of interest.

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Table 1 . Parameters, with a short definition, and all the values analyzed during simulations. The underlined values are the fixed values used in the presented results, while the other parameters varied.

Parameters	Short Definition
G	Compound phenotype size; Length of the binary characters that define each pathogen.
K	Carrying capacity; The pathogen's maximum population size the host can support
σ	Deviation rate for survivor probability; the higher its value the lower the selection pressure imposed by the
b	Reproduction rate; average population growth per reproduction step
μ	Novelty rate per locus, probability of trait state change
p_h	Optimum Phenotype imposed by the host
p_0	Propagule phenotype. It defines the phenotype distance d_0 between propagule and host in the first generati
N_0	Propagule size
	Maximum number of generations that each simulation was run
	Number of simulation repetitions of a given set of parameters.

Legends to figures

Figure 1. Flowchart of the model dynamics. The initial population, with individuals of identical compound phenotype, is subjected to the *Selection* in the newly-colonized host. Upon survival, the simulated pathogen population will then undergo*Reproduction* . The daughter compound phenotype will differ from the parental phenotype according to a pre-defined rate of emergence of evolutionary novelties (μ). Descendent populations are subjected to these cyclic sequences for a pre-determined number of generations

Figure 2. Probability of establishment of the pathogen population as a function of the propagule phenotype distance (d_0). The graphs present the effect of (a) reproduction rate, (b) evolutionary novelty rate, and (c) propagule size (N_0) on the probability of establishment for varying resource distances (d_0). Except for the specifically tested parameter in each graph, the remaining simulation parameter values used are defined in Table 1. The black line in every graph represents the probability of a single pathogen individual of surviving the first reproductive event following colonization at each d_0 - Eq (1). The grey line represents the probability of establishment of the pathogen when all parameters are maximized (the highest values in Table 1) in the simulations.

Figure 3. Evolution of compound phenotype diversity/frequency and population size over generations. Left vertical axis indicate the distance of the pathogen compound phenotype from the optimum value imposed by the host, ($d_{i,n}$), whereas the horizontal axes indicate generation time in simulations. The orange palette depicts compound phenotype frequency in the given generation, warmer colors indicate greater phenotype frequency in the population. The right vertical axis represents the population size, drawn as a blue line - carrying capacity = 1,000 (Table 1). The vertical lines in the last two plots correspond to the respective generation time (same colors) depicted in Figure 3. The respective rates of novelty emergence for each graphic are the following: (a) $\mu = 0.0$; (b) $\mu = 10^{-4}$; and (c) $\mu = 10^{-2}$ - the remaining parameter values are those presented in Table 1.

Figure 4. Maintenance of original phenotypes according to the rate of evolutionary novelties. Relative frequency of compound phenotype as a function of the distance of the pathogen compound phenotype from the optimum value imposed by the host, ($d_{i,n}$) for two levels of evolutionary novelty rates and propagule size: (a) $\mu = 10^{-4}$ and (β) $\mu = 10^{-2}$, $N_0 = 1$ (c)$\mu = 10^{-2}$, $N_0 = 200, b = 7.5$). Each curve represents specific generation times as follow: (a) 45 (yellow line), 120 (dark-orange line), 200 (red line), 500 (brown line); (b) and (c) =10 (yellow line), 13 (light-orange line), 25 (dark-orange line), 35 (red line), 500 (brown line). The first four temporal elements (colored lines) of each list are highlighted by the vertical lines in Figure 3b and 3c, respectively.