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Maria Ines Reinert Azambuja [1]

> ***"Once we recognize that the state of the art is a social product, we are freer to look critically at the agenda of our science, its conceptual framework and accepted methodologies, and to make conscious research choices"*** **(Richard Levins & Richard Lewontin, 1987, apud Krieger, 2001:668 (1)).**

Abstract

The idea of "epidemic constitutions" is attributed to Thomas Sydenham, one of the most eminent physicians of the 17th century. Regardless of the type of disease epidemic (cholera, influenza, smallpox), it aimed to explain what remains unexplained to this day: Why now? And why do some develop serious illness while others do not? In this article, I review some debates that occurred during the cholera epidemics of the 19th century, discuss the idea of telluric "epidemic constitutions", and propose a reinterpretation, or perhaps just an updated interpretation of Thomas Sydenham's amazing insight into the cause of epidemic constitutions: *a confluence between an exciting cause that was in the atmosphere and a predisposing cause that was in the bodies of the sufferers themselves*. With what we have learned since then, I explain his insight as representing the process and product of our co-evolution with Influenza A viruses. I explore theoretically how this interpretation would explain differences in rates and distributions of infection, disease and mortality during epidemics, and, propose alternative explanations to the epidemiology of the early surge of COVID-19 in China and selected countries, based on an epidemiologic inquire on the circulation of influenza viruses during the 2019-2020 influenza season across those countries. The approach brought up new questions that could only emerge from epidemiological (population-based) reasoning (what causes vulnerability?) and epidemiological studies (what was the context of influenza during the emergence of the COVID-19 pandemic?), such as: a) did Influenza B had a role in the production of vulnerability to infection by the SARS-COV2 virus? b) do the SARS-COV2 virus and the H1N1 influenza virus share some immunological attribute conductive to a same type of immune-inflammatory response among non-H1 primed individuals? Or do the sequence B-H1 and B-SARS_COV2

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produce similar morbidity? Does a sequence of B – H1 – SARS-COV2 explain the severity of COVID-19 Pandemic in the US? Do the SARS-COV2 viruses and the H1N1 viruses dispute the same ecologic spot? What would this mean for future developments of our immune-inflammatory landscape?

Key words: Influenza; anticontagionism; causation; epidemic constitutions; COVID-19, H3N2, H1N1; Influenza B; sero-prevalence; mortality; case-fatality; China; United States; Japan, Brazil, Europe.

Introduction

According to Whitbeck (1977) *"The logic of medical thinking includes criteria for selecting certain causally related conditions which answer our instrumental interests in further respects (2, p.619)"*. The context is crucial in determining to which factor we attribute the status of "cause". From the 17th to the 19th century, constitutional theories underpinned the classification of disease types, orienting their clinical treatments and prognoses. Upon the late 19th century's success of the germ theory, classification was adapted to reflect the etiologic agent (2). Like COVID-19 (coronavirus disease of 2019), diseases became frequently named upon the infectious agent associated with them (2), in spite of differences in clinical outcomes of infections by a same agent, and similarities - e.g. acute respiratory distress syndrome (ARDS) - among cases associated with different etiologic agents.

As reviewed by Nancy Krieger (3, pp 97-106), during the early 20th Century, leading epidemiologists from both sides of the Atlantic (Frost, Greenwood, Cruikshank (first IEA chairman)) struggled to call attention to, besides germs, characteristics of individuals (host factors) and populations (proportion of susceptible, "herd immunity") associated with causality. Their efforts did not succeed. Krieger observes, by quoting Greenwood (1935), that, by the time, *"the bacteriological school had become psychologically omnipotent" (3, p. 106).* The decline of infectious diseases' mortality in developed countries along the 20th Century contributed to practically erase this discussion in the following years.

During the second half of the 20th Century, there were at least three documented attempts, by well-regarded US infectious diseases researchers, to reinstate that debate, all unsuccessful:

1- In 1955, Rene Dubos, an eminent microbiologist at the Rockefeller Foundation which *"progressed from ground-braking studies of tuberculosis and pneumonia to investigations of* *the overall pattern of disease, and to the health on earth, to become one of the most influential ecological thinkers of the 20th Century (4, p.66)”*, published a paper called “*Second thoughts on the germ theory: Everyone harbors disease germs, yet not everyone is sick. This is ascribed to “resistance”, suggesting that germs are less important in disease than other factors affecting the condition of the host (5, p. 31)”.* His is a paper worth of re-visitation. ③

2- In 1982, Alfred Evans, an eminent virologist, professor at Yale, published a paper called *“The third ingredient: clinical illness promotion factor”* (6). According to Evans, *“The interaction between a causative agent and a susceptible host involves a series of responses most of which are subclinical or asymptomatic but a few of which are manifested by clinical illness. The factor(s) that tip the balance is (are) poorly understood, in both acute and chronic diseases. (6, p.193)”.* Evans produced a list of factors (age, pre-existing conditions, immune status, pregnancy, stress…) referred (then and now) as being associated with severity of clinical illness among the infected, but he stated that he was not satisfied with that approach. He claimed that marked host variations still existed when all those factors were held constant. Then, he proposed that it must exist something else besides the infectious agent and individual vulnerability, *“a third ingredient”* that, added to the agent and to the vulnerable host substrate, would tip the balance towards more severe clinical illness. He urged epidemiologists to join hands with virologists, clinicians, statisticians, immunologists, biochemists and social scientists to discover this *“third ingredient”* because *“if we could modify it, then our efforts at control and prevention can be directed only at those few persons who develop the disease, rather than at the total group who are exposed as is our current practice. (6, p. 198)”*; and

3- In 1987, Peter Duesberg, an acknowledged virologist, professor at Berkeley, inaugurated with his paper (7) a fierce scientific debate about the role of the HIV in the development of AIDS. In 2009, the journal Medical Hypotheses, forced by defendants of the mainstream idea, of HIV being necessary and sufficient cause to AIDS, retrieved a new paper by Duesberg and cols. The journal's editor lost his position in the process (8). Upon the retrieval, there was an attempt to “excommunicate” Duesberg from the UC Berkeley, resisted by the University.

Alfred Tauber*, “from the perspective of a philosopher and historian of science (9, p.241)”*, does a very interesting distinction between scientific controversies: those that reflect mostly differences in methods and styles of the contenders, and those that reflect differences on how they conceive their object of study. The *“contagionism” x “anticontagionism”* controversy belongs to the second group: the contenders have different ideas about what should be the object of study of infectious diseases: exposure or vulnerability to disease upon exposure (or both), and their determinants.

Contagionism explains *infection in a (vulnerable) individual*, but it cannot explain individuals´ variations in vulnerability, which, at the population level, emerge as variations in rates of infection, morbidity, age-distribution of cases, rates of cases-fatality, and age-distribution of deaths. I am borrowing from Philip Ball a metaphor he discusses in his book *How life works, a user’s guide to the new biology (10)*, originally proposed by David Smithers (1962) against taking a reductionist view on cancer: *“Cancer is no more a disease of cells than a traffic jam is a disease of cars. A lifetime of study of the internal-combustion engine would not help anyone to understand our traffic problems… A traffic jam is due to a failure of the normal relationship between driven cars and their environment (p.408)”.* And Ball goes ahead: *“traffic jams can be triggered by a single individual doing something… But it is doubtful whether this can be identified as the cause of the jam, because a jam will only result if it happens within the right (or wrong) context…the jam is a collective phenomenon that cannot be deduced or predicted from the behavior of a single driver (p.408)”*. This is the exact same point made by Dubois in 1955: *“Weather man lives in equilibrium with microbes or becomes their victim depends upon the circumstances under which he encounters them. This ecological concept is not merely an intellectual game; it is essential to a proper formulation of the problem of microbial diseases and even to their control (5, p.35)”*

As stated by Bachellard in 1972*, “All knowledge is the answer to a question. Without a question, there can be no scientific knowledge. Nothing is spontaneous. Nothing is given. Everything is construction* (11, p.44))”. So, which would be the right question to be posed if one wants to understand a pandemic? To me, it seems that the question would be: what was the context?

This question was posed before, in the 19th Century, in the 17th Century, and possibly at each time when severe epidemics occurred. Thus, this article aims to 1) review the past responses and causal hypotheses to it; 2) reinterpret the main causal hypothesis for epidemics, the epidemic constitution, based on a theory of coevolution between human and influenza A virus populations (12-16); 3) logically analyze the adequacy of this hypothesis to explain each of the features associated with an infectious disease pandemic and identify remaining gaps within the author's original theoretical formulation; 4) document the influenza context and the main features of the COVID-19 emergence in China and explanations to the them during the emergence of the COVID-19 epidemic in China; 5) provide alternative explanations to the observations and new answers to unsolved questions, based on this new theory of influenza-driven epidemic constitutions; 6) discuss the context of epidemics in other countries and provide tentative explanations to some observations, based on this new theory; 7) present new questions regarding the COVID-19 Pandemic brought by this approach; 8) discuss the challenges and opportunities brought by a new perspective on infectious (and non-infectious) diseases´ causality.

Everything that I am proposing here is far from the state of the art of our scientific agenda. I do not expect to be right every time. What I expect is that you may read these ideas as once suggested by Bacon: *“not to contradict nor to believe, but to weight and consider (17, p.4)”*. Even if they were wrong, they sure open new possibilities to be explored by fellow scientists, more consonant with the advancing evolutionary perspective of population biology (10, 18-23).

Method

This paper required

1) A review of historical records of epidemiologic observations and debates happening during earliest pandemic periods, obtained from Creighton (24), Ackernetch (25), Rosen (26), Cairns (27), Krieger (3), and several papers that, thanks to George Davey Smith and Shah Ebrahim (28), editor and co-editor of the International Journal of Epidemiology from 2001 to 2016, were made available to the readers through a section called “Reprints and Reflections”;
2) a description of the Influenza H1, H3 and B viruses’ circulation in the 2019-2020 season in selected countries, based on data from the WHO-FLUNET (29) (view the annex);

3) a description of the early evolution of COVID-19 mortality in the same countries, obtained from www.ourworldindata.org (30) (view the annex);
4) a review of features associated to the emergence of the Pandemic and China, and unsolved questions;
5) a review of features associated to the emergence of COVID-19 Epidemics in Europe and unanswered questions, and
6) the tentative provision of answers to the still unanswered questions, and the proposition of new questions.

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1. Historical review: Anticontagionism

"Historians usually give a biased account of the heated controversy that preceded the triumph of the germ theory in 1870 (5, p, 31)" The 19th Century debate on causes of epidemics had nuances that went beyond the simplification and opposition implied by the word *anticontagionism.* The so-called *anticontagionism* had two branches: one ''localist'', ''miasmatist'', and sanitary reformer and other identified with "tellurism" and the Hippocratic notion of "atmospheric conditions" (3, 25-28). Between 1820 and 1845, Villermé, in France, and Chadwick and Engels, in England, provided detailed descriptions of both economic development and worsening workers' living and health conditions associated with Europe's industrialization and urbanization (25-27). Three cholera epidemics, tuberculosis, pneumonia and influenza accounted for a high burden of young-adults' deaths (27) and infant mortality was a sensitive marker of social and environmental differences (31). According to Ackerknecht (25), based on empirical evidence plus the sociological theory rooted in the enlightenment, the "miasmatists" attributed variations in the amount and distribution of deaths to a *'social epidemic constitution'*. The so called "tellurists" admitted that bad sanitary conditions, overcrowding and bad water were invariably connected with fatal cholera outbreaks, but they postulated that people permanently exposed to unhealthy environments died from cholera *only after the addition of a temporary epidemic influence* (25-26, 32-33). They believed in a *'physical epidemic constitution'* associated with variation in some undetermined atmospheric condition (25-27, 32-33). Towards the second half of the 19th Century and the beginning of the 20th Century, *'contingent contagionism'*, a synthesis between contagionism and anti-contagionism (3, 25-26, 33) best represented the ideas of medical doctors and public health officers in Europe (Edwin

Chadwick, John Sutherland, John Simon, Rudolf Virchow and Max von Petenkoffer) (3, 25-26) and the US (Wade Hampton Frost and Edgar Sydenstryker) (3, 26). According to them, contagion had a determinant role in the spread of infection, but it could neither account for the epidemics nor for the patterns of distribution of severe cases and deaths in the population. It could act only in conjunction with other elements – like the state of the atmosphere, the conditions of soil and social factors (3, 25-26, 33).

During the COVID-19 Pandemic, once again the *"social epidemic constitution"* proved determinant to the distribution of morbidity and mortality. My interest, however, is to review the idea and evidences in favor of the then-called *"telluric epidemic constitution"*.

1.1 ***The Telluric Epidemic Constitution***

John Sutherland' s ideas about what caused the 1848-49 and the 1854 Cholera epidemics in London, brought to us by Davey Smith (33), Hamlin (34), and SJ Snow (35), and specially Hamlin's commentary on John Sutherland's epidemiology of constitutions (34), were fundamental to my interest in resuming this historical discussion.

In 1848, in London, both John Sutherland (36) and John Snow (37) had empirically shown the association between contaminated water and cases of cholera. However, while Sutherland accepted that contaminated water caused *cholera cases*, he always disputed the idea that it caused *cholera epidemics*, as defended by John Snow. Sutherland argued that contaminated water or bad sanitary conditions *could not explain the outbreaks* themselves *or the age-pattern of the severely ill* (50% of hospitalized cases were between 20-40 years of age (25, 34- 36). Hamlin tells us that, to Sutherland, 'cholera' was a matter of degree, a construct designating a certain set of symptoms and a disease course. Sutherland's question was why did the course of symptoms sometimes lead to deadly sequelae (cholera) and sometimes resolved safely? As posed by Hamlin, *"Factors that influenced the course of disease, then, were causes, not of the disease itself in a modern sense, but of its course and outcome (death or recovery), which was, after all, from the patient's point of view, the most important* matter (34 p.916)*"*. Sutherland suggested that the role of contaminated water was one of a "localizing agent" that, by producing cases, unveiled *the true cause of the epidemic*: an *'epidemic constitution'*. (34-35). As explained by Hamlin (34), the concept of *'epidemic constitution'* had a dual meaning: it referred to *something that transiently existed in the air*, but it was also applied to *a particular population* *pattern of individuals' vulnerability unveiled by the epidemic*, expressed, for example, as stated by Sutherland, in the age-distribution of cases and in the varying courses of disease, from mild presentations to death (34-36). According to Johnson (38), this is how Thomas Sydenham, one of the most important medical doctors of 17th century and main proponent of an internal-constitution theory of epidemics, describes it: *"Certain atmospheric conditions were likely to spawn epidemic disease, but the nature of the diseases that emerged depended partially on a kind of preexisting condition, a constitutional susceptibility, to smallpox, or influenza or cholera".* A distinction is made between exciting and predisposing causes. "*The exciting cause was the atmospheric condition that encouraged certain kind of disease: a specific weather pattern that might lead to yellow fever, or cholera. The predisposing cause lays in the bodies of the sufferers themselves (38, p.132)*".

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2. Re-interpreting the evidence: towards an infectious immune-inflammatory theory to epidemic constitutions

The concept of *"epidemic constitutions"* may be traced back to Sydenham (a medical doctor) and Boyle (a chemist) in the 17th Century, and even to Hippocrates, to explain *"the mysterious something which had to be assumed so as to explain plague, pestilential fevers... and all other epidemic constitutions which were not caused by obvious changes of season and weather* (24, p.400)". By then, it was reasonable to associate it with some type of chemical emanation or atmospheric modification (24-25, 33). Nowadays germs give us an alternative.

2.1. Previous developments

I have proposed, since 2004, that the influenza A viruses and we, humans, have co-evolved *as populations* (12). As the influenza A virus population changes (39-40), the immune-inflammatory landscape of the human population also changes, and the dynamic of this continuous interaction would be a motor to our evolving population constitution (12, 14-16). This, I believe, would explain secular variations in levels of morbidity and mortality, secular variations in types of diseases' and deaths' occurrences (e.g.: the early 18th Century decline of Tuberculosis mortality, the early 20th Century decline of acute infectious diseases mortality, the 20th Century rise and fall of ischemic heart disease mortality, the rise of diabetes/obesity, the AIDS epidemic and other variations in occurrences) (14-16), and also partially explain the variations in rates of birth over time (14,41) This evolutionary theory to epidemiologic change is rooted in my initial attempt to explain the birth-cohorts association that I found, in 1993, between the 1918 Influenza mortality and the 20th Century rise of CHD mortality (42-50).

Before explaining the theory, a brief review about influenza is necessary.

2.2. Influenza

Influenza viruses have co-existed with us for centuries (24). Infections are recurrent and have an annual interhemispheric cycle with strong seasonality in temperate latitudes (40, 51-52). All of us remember having several episodes of influenza, some light and some with significant inflammatory effects (fever, muscle pain, headache). Most symptomatic cases course with upper respiratory symptoms and resolve in 5-7 days (40, 53), however, mortality by several causes (respiratory, cardiovascular, neurologic) increases during or just after rises in seasonal influenza occurrences (54). Two main types of influenza infect the human population: influenza A and influenza B. Both types cause seasonal epidemics with clinical presentations of infection largely indistinguishable, young children and the elderly being more susceptible to infection (40, 53-54). Very good reviews of Influenza are available (40, 53), so I will present just a few aspects as underpinnings to the discussion ahead.

2.2.1 The influenza B viruses

The influenza B viruses were first isolated in 1940. Two lineages emerged during the 1970s, B-Victoria and B Yamagata (40,55). Since 2011, the Victoria lineage has diversified, first into 2 dominant clades (55), and after 2016-17, through amino acid deletions, into additional variants: B/VIC V1A (no deletion), B/VIC V1A.1 (two-AA deletion), and B/VIC V1A.2 and V1A.3 (three-AA deletion) (56).

Influenza B virus have been less studied than influenza A virus because they historically caused fewer and smaller epidemics and no pandemic (51).

2.2.2. The Influenza A viruses.

The human type A influenza virus was first isolated in 1933 (57). The majority of research on influenza focuses on influenza A viruses, owing to the diversity of species that they infect, their burden to reared livestock populations, their ability to cause global pandemics in humans and their substantial contribution to the human burden of diseases and deaths during the influenza season (40, 51). Influenza A viruses are further classified into subtypes based on combination of their surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). Only three combinations have circulated widely in humans during the last century: A/H1N1, A/H2N2 and A/H3N2. Influenza viruses suffer two types of antigenic changes: 1- *antigenic drifts*, which are gradual minor genetic changes of HA and NA produced during replication, resulting in variant strains of the original virus; and 2- *antigenic shifts*, which are major antigenic changes produced by reassortments of viral genes between human and animal viruses, leading to the replacement of the circulating influenza A virus by a new subtype (40, 51, 58-60). Analyses of influenza shifts show that novel NA and internal genes are introduced into the prevailing human virus strains before acquisition of the novel pandemic HA. However, *it is the acquisition of the novel HA that marks, with a pandemic, the emergence of the new subtype* (61). Based on viruses' isolation, and on sero-archeologic studies that attempt to reconstruct the periods of circulation of different Influenza A subtypes before its first isolation, the current consensus (51, 58-60) about the time of introduction and period of circulation of successive influenza subtypes (here represented by their hemagglutinins) is: **H3 - 1890 pandemic**; **H1** from the **1918 pandemic**-57; **H2** from the **1957 pandemic**-68 and **H3** from the **1968 pandemic** –2025. In **1977**, an **H1** virus identical to the one that produced epidemics in 1951 (51) re-emerged. It disseminated globally but because disease was mild and restricted to those less than 25 years of age (59), the increase in cases was not called a Pandemic. Interestingly, the 1977 H1 virus did not eliminate the circulating H3 (51, 58-60), what initiated a first observable period of global co-circulation of two influenza subtypes (51). The **2009 H1 pandemic** resulted not of a change in a circulating subtype, but of a substitution of the circulating H1 by a new H1 reassortant strain (62). The new **p2009H1** and the **H3** subtypes continued to co-circulate, with variations in occurrences from one to the next influenza season and, within the same season, among different countries (63).

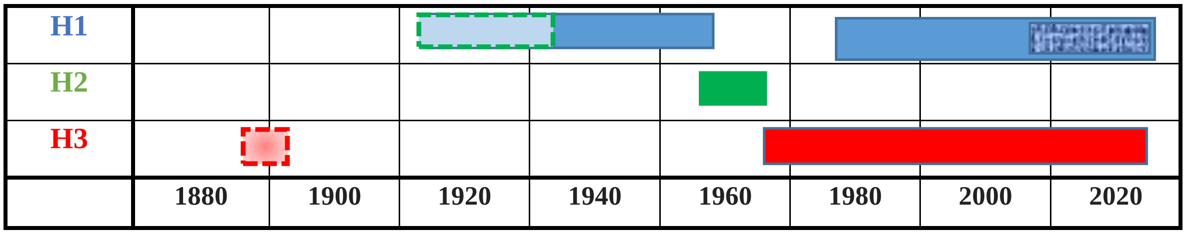

Fig.1- Introduction and period of circulation of influenza A subtypes. (solid colors- observed; watery colors – inferred; patterned blue – p2009H1).

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2.2.3. Biologic phenomena associated with influenza A infections

Three well known phenomena associated with influenza A infections constitute the underpinnings to my theory (33):

1- The *original antigenic sin*, recognized since 1953 (64) and so described by Davenport et al. in 1969 (65): *"the major antigens [subtype] of the [influenza A] strains of first infection of childhood permanently orient the antibody-forming mechanisms so that, on subsequent exposures to influenza viruses, the cohort of the population would respond with marked reinforcement of the primary antibody (65, p. 453)"*. This mechanism would explain, for example, the low rates of severe disease shown by very old individuals, during the 1969 H3 Pandemic (66), and by individuals older than 60 years of age during the 2009 H1N1 Pandemic (67): their antibody forming mechanisms were prepared to positively react against those viruses, because they were similar to the ones associated with their first influenza experience.

2- the *recycling of influenza A viruses superficial antigens*, meaning the re-introduction in the population, from time to time, of subtypes of the influenza A viruses antigenically similar to viruses that circulated in the past. Supposedly, anti-influenza antibodies accumulating within the human population would restrict the spread of strains antigenically alike their recent predecessors. On the other hand, the possibilities of viable variations of influenza A antigens would be limited (65). Together, these conditions would favor the recycling of old influenza sub-types (58,65,68). Viruses associated with the 1957 (H2) and the 1968 (H3) pandemics are examples of recycling of antigens prevalent at the end of the 19th century and at or about the turn to the 20th century. According to Dowdle (58) the H3 subtype that emerged in 1968 recycled antigens from the 1890 Pandemic virus. There is no consensus about the exact periods of circulation of H1, H2 and H3 sub-types after 1890 until the 1918 Influenza Pandemic (58-59, 65-66, 68-69).

3- *Hetero-subtypic immune responses to reinfections.* Thomas and cols (70) showed that, after a secondary challenge with a different influenza virus, hidden epitopes may emerge and switch protective immunity to an alternative antibody-mediated pathway. Chen and cols. (71), studying immunity to influenza A virus in mouse models of respiratory viral infections, showed that *‘‘heterologous immunity induced two patterns of disease outcome dependent on the specific virus infection sequence: improved, if the acute response switched from a neutrophilic to a lymphocytic response or worsened, if it switched from a mild to a severe lymphocytic response”* (71, p. 1341).

2.3. Influenza recycling and epidemic constitutions: an evolutionary theory to epidemiologic change

> ***“Don't multiply the mysteries - I say. - These must be simple. Remember Poe's stolen letter, remember Zangwill's locked room. - Or complex - replied Dunráven. - Remember the universe.”*** *JL Borges quoted by LF Veríssimo (72)*

Every year, influenza A viruses infect a part of the human population. We do not know its size because most influenza infections are a- or low-symptomatic, and underreported (73). Each emerging influenza A sub-type usually persists for several years priming naive individuals (new birth-cohorts) and re-infecting those from cohorts previously primed by the same or a different subtype. Over the years, the subtypes recycle. The original antigenic sin establishes a birth-cohort pattern of immune “pre-configuration”. I propose that *transient activations* of those pre-configurations vary with the subtype(s) producing influenza re-infections. Infection by the same subtype that originally primed the earliest birth-cohorts would be non-inflammatory and produce low morbidity among individuals belonging to those cohorts, but priming and re-infection by different subtypes would produce some *specific* transient immune-inflammatory effects capable of enhancing vulnerability to disease expression (morbidity). At each moment, the population landscape of (transient expression of) immune-inflammatory phenotypes would be contingent to the subtype(s) that circulated during the last influenza season, varying with the population history of the birth-cohorts’ priming. At the population level, this process would produce an ever changing immune-differentiation (evolving population constitution) and cycles of vulnerability to different diseases over time (14-16).

2.3.1 Influenza *and the 20th Century rise and fall of CHD mortality*

To explain the association between the age (birth-cohort) distribution of the 1918-19 influenza mortality and the 20th Century rise of CHD mortality, I proposed that, in the same way that re-infections by Group A β-hemolytic streptococcus reactivate valvar inflammation and induce rheumatic heart disease progression, re-infections with H1 (and H2) influenza viruses (circulating until 1968) reinforced inflammatory pathways to CHD established by hetero-subtypic immune responses induced by infection with the 1918 H1 Influenza A virus, of H3 primed individuals born around the 1890 H3 Influenza Pandemic (44-50). Consider that atherosclerotic lesions happen in areas that receive the highest loads of both viruses and immuno-inflammatory products from the infected lungs: the left side of the heart, the coronary arteries, and the aortic arch with its main branches (44, 46, 50).

2.3.2. Influenza and the decline in CHD mortality

In 1968, when the H3 influenza subtype re-emerged, CHD mortality started to decline. It fell 56% from 1968 to 1999 in the US (74-75). However, the fall was not just due to the re-emergence of the H3 subtype. Maybe more important was the transition of ‘original antigenic sins’ from H3 to (H2 and) H1 influenza primings towards the beginning of the 20th Century (65-66, 68-69). The immune-inflammatory landscape had changed. The H3 viruses that re-emerged in 1968 were re-infecting not only H3 primed birth-cohorts, but also non-H3 primed ones. CHD declined but respiratory diseases, obesity and diabetes increased, and a second atherogenic phenotype (low HDL, high triglycerides) was unveiled among persisting CHD cases, suggesting CHD to be more than one disease (46-48).

2.3.3. Reinforcing evidences of auto-immune activation and morbidity associated with the recycling of influenza A antigens

Recently, several papers have brought additional evidence to this interpretation. Zangh and cols. (76) reviewed the subject in 2019 (without reference to my work). Linderman and cols. (2014) (77) found that middle age individuals born from 1965-79 were highly susceptible to H1N1 viruses during the 2013–2014 influenza season (they did not made the association, but those were years of Influenza priming by H2 or H3 sub-types). Gagnon and cols. (2018) (78) showed that early life H2N2 influenza infection enhanced susceptibility to death during the 2009 H1N1 Pandemic. Flannery and cols. (2018) (79) found that during 2015–2016, A(H1N1)pdm09-specific vaccine effectivity was 22% (95% CI, −7%–43%) among adults born from 1958–1979 (primed by H2 and H3 influenza sub-types) versus 61% (95% CI, 54%–66%) for all other birth cohorts combined. Skowronski and cols (2019) (80) reported a paradoxical sign of increased (rather than reduced) risk of illness upon infection by influenza A(H3N2) clade 3C.3a among those vaccinated with influenza A(H3N2) clade 3C.2a / 3C.2a1 compared to non-vaccinated adults in Canada. They hypothesized an underlying cohort effect of the 1968 A (H3N2) pandemic: vaccine mismatch might have negatively interacted with the imprinted immunity of the original antigenic sin. They also reported the observation of the Canadian Sentinel Practitioner Surveillance Network, of a prominent shift in the age-distribution of influenza A (H1N1)2009 cases in the 2018-19 influenza season (H3 dominated), with more children younger than 10 years-old among the cases. They postulated an immunological cohort effect following the 2009 influenza A (H1N1).

3 – Further characterizing "epidemic constitutions" and their determinants under this new the immune-inflammatory interpretation

"In science, power springs from abstraction" (Atkins P, 81 p.50)

An infectious disease results from a sequence of events comprising exposure, infection upon exposure and disease upon infection. This is a generic/universal way of describing the steps required to produce a case. When we move from an individual to the population, each of these steps become probabilities of occurrence: **of exposure, of infection upon exposure, of disease upon infection and of severe cases/deaths upon disease**. An epidemic implies increases in these probabilities. Thus, it would be correct to say that everything that increases them is a cause and contributes to conform the "epidemic constitution". Within this framework, a causal model that explained the inception and early evolution of the COVID-19 epidemic in China and Europe could be written as the product of interactions among the probabilities of the determinants shown below:

Population
X
probability of exposure to the SARS-COV2 virus

= ***number of exposed***
X
probability *of population vulnerability* to *infection, upon exposure*

= ***number of infected***
X
probability *of population vulnerability to disease, upon infection*

= ***number of symptomatic cases***
X
probability of *vulnerability to severe illness and death among the sick*

= ***number of severe cases/ deaths***

This *causal model* supposes that each probability (rate of occurrence) has their own biologic determinants, which may vary over time. Because the population effects of those probabilities of occurrence are multiplicative, we would expect huge decays along rates of infection, morbidity and mortality. The expectedly non-random (contextual) nature of the distribution of those biologic determinants would result in varying epidemic presentations (from large to small, with high morbidity and low mortality, with low morbidity, with high cases-fatality, etc.).

3.1. Exposure

We are bombarded with many infectious agents all the time, but pandemics are relatively rare events. Thus, how to explain the inception of one? As the SARS-COV-2 virus is a new zoonotic agent, we tend to attribute the emergence of the COVID pandemic to the emergence of (and exposure to) the new virus. However, experience with other pandemics suggests that we should be cautious about assuming that the virus is a necessary and sufficient cause for starting a pandemic. Sutherland asked, in the 19th Century, why now? If the Thames River was polluted all the time, why cholera epidemics emerged in London as part of global pandemics, in 1831-32, 1848-49 and 1853-54?

3.2. Infection upon exposure

Maybe well-adapted human pathogens like those associated with Typhoid, Cholera, Dengue and Yellow Fever might produce epidemics if an epidemic constitution raised the probability of morbidity and mortality across particular ages/birth-cohorts' strata. An increase of severe cases would produce epidemiologic awareness that would promote the identification of mild and asymptomatic cases and an epidemic would soon be declared. But would this be enough for a new agent like the SARS-COV2 virus?

A new virus would hardly emerge well adapted to produce infection in humans. For an emerging zoonotic agent to produce a human pandemic, it is reasonable to suppose that something in the "epidemic constitution" would increase the *probability of infection upon exposure*, increase the individuals' vulnerability to a still not well adapted pathogen, until it evolved and adapted itself. (Or not. Consider the rarity of global pandemics compared with the number of episodes of aborted events that we had in the last years - SARS, MERS, Zika, and Ebola).

3.3. Disease upon infection

The effect of any infection depends on the immune-inflammatory configuration of the host, or we would not have such high rates of asymptomatic and mild cases of SARS-COV2 infection during the pandemic. I proposed above that two well-known phenomena associated with Influenza A infections - the *recycling of influenza A antigens* and the *"original antigenic sin" (OAS)* – would produce secular variations in the occurrences of different diseases (14-16). Influenza A viruses, at the same time that prime new naïve birth-cohorts to future adaptive (non-pathogenic) responses to re-infections with the same subtype, would transiently activate pro-inflammatory states in individuals belonging to birth-cohorts previously primed by a different subtype (14-16) This would occur continuously in the population. The population pattern of immune-activation produced by the last encounter with an influenza A virus would result in the type, size and age/birth-cohort distribution of the transient immune-inflammatory effect.

Sydenham proposed, in the 17th Century, that the disease that emerged as an epidemic depended on a preexisting condition, *a specific constitutional susceptibility, to smallpox, or influenza or cholera.* "*The exciting cause was the atmospheric condition that encouraged certain kind of disease: a specific weather pattern that might lead to yellow fever, or cholera. The predisposing cause lay in the bodies of the sufferers themselves (38, p.132)*".

Under the hypothesis proposed here, this would occur if 1) different sequences of individual´s priming and last reinfection by influenza A viruses activated different immune-inflammatory phenotypes (BOX 1), and 2) if different immune-inflammatory phenotypes varied in reactivity to different subsequent environmental challenges.

BOX 1. Modelling Immune-activation upon influenza A reinfections of influenza A primed birth-cohorts

OAS	INFLUENZA RE-INFECTIONS	
	H1	H3
H1	no activation	phenotype 3
H2	phenotype 1	phenotype 4
H3	phenotype 2	no activation

OAS - Original Antigenic Sin

In summary, I propose that the landscape of actionable immune-inflammatory phenotypes within the human population is constantly evolving, but which phenotypes will be activated *next*, through which ages (birth-cohorts), and with which effects, would depend on, besides each population's history (subtypes circulating in the past), the subtype(s) circulating in the next influenza season. Dubois, in 1955, had already said that *"susceptibility to infection is not necessarily inherent in the tissues, or dependent on the presence of antibodies, but is often the temporary expression of some physiological disturbance (5, p.34)"*.

3.4. Severe disease among cases – cases-fatality

According to Morens and Taubenberger (82), in 1918, Influenza was clinically unremarkable in 98% of infected persons. In 2006, upon the reconstitution of the complete genomic sequence of one virus e partial sequences of four other obtained from archival influenza autopsy materials collected in the autumn of 1918 and recovered in 1995, they found no known mutations correlated with high pathogenicity in the samples (83). They would continue looking for genetic features of the 1918 virus, but acknowledged the need to also examine the host and environmental factors (83). Both papers (82 and 83) reproduced graphs of the age distribution of morbidity, case fatality and mortality in 1918-19, and concluded that we were no closer to understanding the epidemiology of the 1918 Pandemic than Frost (84) in 1920 and Britten (85) in 1932, who presented the same graphs based on a survey done in late 1918.Pandemic in 12 US locations.

In 1920, Frost discussed *"highly important relations between morbidity and mortality, which must be borne in mind in applying mortality 'statistics' of the epidemic" (84, p. 597)*. In

1932, Britten further detailed those relations. The survey had shown 30% (15-53%) of cumulative incidence of *symptomatic* cases of influenza and pneumonia from September to the end of the autumn-winter wave of the pandemic. The incidence was highest among the young (5-9 years of age) with a small secondary peak at about 30 years. The attack-rate fell off rapidly in older life. Cases-fatality by age varied from 0.8 to 3.1%, with no association with the incidence rates. It was high in children less than 5, from ages 20-40 and over age 60 (see Fig 1). Cases-fatality was associated with pneumonia. Pneumonia occurred in 6% of the total cases (incidence of 17/1000 population), but it attained incidences of 10-30% among young adults. Pneumonia cases-fatality did not show a striking increase in young adults. According to Britten, it was the very high *incidence* of pneumonia in young adults, and not differences in pneumonia cases-fatality, the most important determinant of the age-mortality curve (85).

There is a discussion in the literature about the etiology of the 1918 pneumonia cases. While Morens and Taubengberger (2012) attribute most cases to superinfection of a viral pneumonia with bacterial agents (82), Crosby (1989) reports that sir MacFarlane Burnet, a 1960 recipient of the Nobel Prize for Medicine, had already proposed that the disproportionate increase in pneumonia (ARDS?) in young adults in 1918 should be attributed "*not to the virus, but to a stronger immuno-inflammatory response expected in those individuals at ages commonly called the prime of life (86, p.221)"*. Others, myself included, agree with his immune-inflammatory hypothesis, but had an alternative explanation to it: immuno-pathogenic inflammatory reaction triggered by an inefficient immune response to infection with H1 influenza viruses of individuals belonging to birth cohorts primed by H3 influenza viruses associated with the 1890 pandemic (12-14, 45-46, 87-88).

However, I noticed that a conundrum emerged when I attempted to conciliate this explanation with what my general hypothesis which proposes: that H1 re-infections of H3 primed birth-cohorts would increase the occurrence of **cases upon infection**, the influenza **morbidity**, the unexpected secondary peak in the age-distribution **of cases** around age 30 *(fig.1). Logic and the numbers do not fit to the idea of it being responsible for the rates of* ***deaths*** *(= morbidity x* ***cases-fatality)***. In 1918, symptomatic cases of influenza were detected in 34% the individuals born around the 1890 pandemic (25-29 years in 1918). This morbidity rate makes sense if we assume, for example, a 60% rate of H1 re-infection of individuals belonging cohorts born around 1890, 60% of them primed by H3 viruses around the time of the 1890 H3 pandemic

(0.6X0.6=0.36), or something like that. But why, from 34% of symptomatic cases at ages 25-29, deaths occurred in 3% of them? Such a decay would require an additional supervening determinant, with a probability of occurrence of at least 10% among the cases (0.34 X 0.1 = 0.03) … [just an illustrative possibility]. Which could it be?

From the time when the human influenza A viruses were first isolated (1935) until 1977, we documented their continuing circulation in our population, one subtype at a time. We assumed that this was how the virus behaved since at least 1918: that a virus of the same subtype of the ones isolated after 1935 emerged in 1918 and continued to circulate until being substitute by an H2 virus during the 1957 Pandemic. Only after 1977 we observed the concurrent circulation of two influenza subtypes, the H3 that had emerged in 1968 and a re-emergent H1 very similar to the one circulating in the late 1950s, which resurfaced by 1977 (51).

During the 2009 influenza pandemic, p2009H1N1 and seasonal H3N2 co-circulated and, at that time, I proposed that ***co-circulation might have increased the occurrence of cases´ severity*** (67). As much as I know, the scientific community has never considered the possibility of co- or successive infections by two influenzas A virus subtypes to be causally associated to the 1918-19 pandemic mortality. However, and I will return to this later, co-circulation may be the best explanation to the non-correspondence between the age-distributions of morbidity and mortality during the pandemics, and the need for co- or successive infections the best explanation for the decay between rates of symptomatic and rates of severe influenza cases and deaths in the autumn of 1918, and in 2020.

It has been shown that multiple respiratory viruses can concurrently or sequentially infect the respiratory tract of individuals (89). Infection by a first virus could enhance or reduce infection and replication of a second virus, resulting in positive (additive or synergistic) or negative (antagonistic) interaction. The concept of viral interference has been demonstrated at the cellular, host, and population levels. But we have very few studies on this subject so far.

3.5. Summarizing

An epidemic requires, besides the population *Exposure* to the agent of interest – currently our main focus of research – an *Epidemic Constitution*, meaning the “contingent interactive terrain” encountered by the Exposure, which will (or not) allow that infection emerges, define the size and velocity of its transmission, its associated morbidity rate and the age-distribution of the cases, and the size and distribution of cases´ fatality. Here we will be focusing upon the biologic determinants of the epidemic constitution, without losing sight that both, the exposure and each epidemics' *"contingent interactive terrains"*, as much as the resources to confront their effects, are also historically, socially, economically and politically determined.

4. The 2019-20 Influenza season and the COVID epidemic constitution in selected Countries

4.1 The 2019-2020 Influenza Season

H1N1 and H3N2 influenza A subtypes are called A1 and A3 in the figures.

Fig. 3 presents the weekly rates of identification of influenza A1, A3 and B (Victoria) viruses during the 2019-2020 influenza season in China and in countries selected by their different COVID-19 experiences during the early development of the Pandemic (Korea, Singapore, Japan; Iran; Italy Spain, France, UK, Portugal; US). For the production of the figures, see the Annex.

Fig. 3 shows that the circulation of all influenza viruses declined sharply around weeks 5-6 in China, Singapore and Korea, possibly due to the lockdown enforced in those countries. Japan already had lower circulation of influenza viruses in early 2020 compared with previous years (see ahead). In Europe and the US, influenza circulation persisted for additional 3-4 weeks after the declines in Asia.

4.1.1 Influenza B

I initiated this investigation focused on Influenza A viruses. A completely unexpected finding was how <u>smaller was the influenza B Victoria circulation</u> in countries with <u>low early COVID-19 mortality</u> (Korea, Singapore, Japan).

Figure 4a displays 3-weeks moving averages of rates of weekly influenza B virus isolations relative of all processed samples (influenza positive and negative), in selected countries (see the Annex). Fig 4b displays the early evolution of the number of deaths, and fig. 4c, of mortality rates, by COVID-19, in those same countries (see the Annex). According to the data, Portugal, Iran and the United States had the earliest rises in the circulation of B viruses in the 2019-2020 Influenza season. In Portugal, the initial high level was followed by an early decline, that might have prevented influenza B infections of contributing to the COVID-19 epidemic constitution. In the US, like in Portugal, the 2019-2020 influenza season had an exceptional early surge of influenza B, followed by increasing rates of circulation of influenza A1. But, in the US, the virus B continued to circulate with H1 viruses until the end of one of the most protracted seasons recorded (90) (see Fig. 3 and discussion ahead). In Iran, the rise of influenza B occurred towards the end of the influenza season, with low co-circulation of A1 and A3 Influenza viruses (Fig 3).

In the European countries, except for Portugal, the order of the rising rates of influenza B identification, early in 2020, predicts well the order of increases in COVID mortality some weeks later (figs. 4b and 4c). Italy and Spain first, followed by France and Sweden. In the sequence, it comes Germany, with proportionally lower rates of influenza B and of lower levels of deaths from COVID-19. Co-circulation of B and A viruses occur in all these countries. As for the UK, the time of inception and length of the first COVID-19 mortality wave correlates well with the period of increase of rates of influenza B detections, but the reported level of influenza B detections was lower than expected if it were to explain alone the rise in UK COVID-19 mortality. But like China, the UK had a huge previous wave of Influenza A3 (see ahead). Japan is not represented in the figure 4a because the WHO FLU-NET did not display the country's total weekly number of processed samples (positive plus negative) used to produce the estimate. However, Figure 3 shows Japan's small rate of influenza B isolates among the weekly positive influenza samples, and Fig 4b the country's early low numbers of COVID-19 deaths. Low rates of Influenza B detection and of early number of COVID-19 deaths also happened in Korea and Singapore.

Thus, generally, there was an unexpected correspondence between the sequence and sizes of rises in rates of influenza B isolations after the turn to year 2020 and the sequence and sizes of early rises in COVID-19 mortality weeks later, across the countries.

New hypothesis: may a previous infection with an Influenza B virus have increased the odds of infection upon exposure to an emergent, non-adapted, SARS-COV2 virus? And/or increased vulnerability to mortality, upon infection?

4.2 China's 2019-2020 Influenza season and early development of the COVID-19 Epidemic

Fig. 5 shows estimates of the weekly circulation of influenza viruses in China during the 19-20 Influenza season. The lines show the weekly rates of identification of influenza B

(Victoria), A H1 and A H3 viruses per 100 submitted samples (influenza positive and negative) (29, see the Annex). We see that A H3 and B viruses increase their rates of circulation at the end of November-beginning of December. The A H3 circulation grows faster, attaining its highest rates in weeks 52/2019 to 01/2020 and then initiating a fall. Influenza B grows slower and reaches its heights (lower than influenza A H3) by January 19. The A H1 subtype increases its circulation about two to three weeks after the influenza B, by December 12. Circulation of A H1 and B viruses continue to increase as circulation of the A H3 declines. Influenza A H1 virus attains the same heights of influenza B one week later - by Jan 27 – when Influenza B starts to fall. All the 3 viruses fall together after Jan 31, the A H1 virus with a small delay relative to the A H3 and B viruses.

The WHO-FLUNET data on influenza circulation for the whole country seems to adequately represent trends in the north and south regions (91), and Wuhan (92). According to the Technical Manual of Chinese National Influenza Surveillance, the Hubei province belongs to the Southern China, but it is at the frontier between the South and North regions. In the 2019-2020 Influenza season, in Southern China, Influenza B isolations may have increased faster and surpassed influenza A3 isolations earlier, around Jan 20, but the North and South isolation trends for the three viruses were similar (91).

In fig.5, superposed to the influenza trends is a figure displaying the 72,314 COVID cases identified through February 11, 2020 by day of symptoms' onset, published by the China's Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (93-94) The *COVID cases* are displayed within four diagnostic categories: confirmed in blue, suspected in green, clinically diagnosed in yellow and detected asymptomatic in red. A zoomed-in view of all days in December, when total daily COVID cases count remained below 24, is also displayed (93-94). COVID-19 cases (diagnosed) remained at very low numbers at first. Numbers began to increase as influenza B continued to increase, and accompanying the rise in the circulation of influenza A1. The epidemic (measured by the evolution in the number of cases) grew faster from January 10 to Jan 22. New cases peaked and hit a plateau between January 23 and 27 and steadily declined after that (93-94).

Also in Fig.5, a red line depicts the *evolution of COVID-19 cases-fatality* in Wuhan, published in the Report of the WHO-China Joint Mission (93, p13). Cases-fatality falls from 17.3% for cases with symptoms onset from January 1-10 (small number of cases) to about 12%

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from January 11-20, 7% from January 21-31 and 0.7% for patients with symptoms onset after February (93).

Summarizing, Fig. 5 shows that COVID-19 cases rose during the rise in circulation of influenza B, and accompanying the increase in circulation of A1 influenza viruses, and cases' fatality declined with the fall in circulation of A3 viruses.

4.3 The COVID-19 Epidemic - Early events in China

This section highlights the main points identified and discussed during the emergence of the Covid-19 epidemic in China, and proposes explanations to them based on the hypotheses presented in the previous sections. Unless stated otherwise, they were extracted from two sources: a Report of the WHO-China Joint Mission on Coronavirus Disease 2019, 16-24 February 2020 (93) and a paper published by the Novel Coronavirus Pneumonia Emergency Team, from the CDC China (94). Both refers to the same data. The CDC-China published it as a retrospective analysis of all cases of COVID-19 diagnosed nationwide in China by February 11, 2020: 72,314 patient records—44,672 (61.8%) confirmed cases, 16,186 (22.4%) suspected cases, 10,567 (14.6%) clinically diagnosed cases (Hubei Province only), and 889 asymptomatic cases (1.2%). Up to Feb 11, 1,023 deaths occurred among confirmed cases for an overall cases fatality rate of 2.3%. The epidemic spread outward, from Hubei Province, sometime after December 2019, and by February 11, 2020, 1,386 counties across all 31 provinces were affected (94).

Features highlighted in the reports during the emergence of the COVID-19 cases in China

4.1 - The virus had a zoonotic origin, and the Huanan Wholesale Seafood Market was the probable source of the viral spillover (WHO, CDC China);

4.2- Susceptibility to the SARS-COV19 was expected to be universal, once it was a new pathogen and there was no pre-existing immunity in humans (WHO);

4.3 - *"Of note"* was the highly clustered nature of local transmission, with high R0 (2-2.5) within families and closed settings like long-term living facilities, hospitals and prisons, but low population case counts. (WHO)

4.4 - Transmission occurs via droplets and fomites during close unprotected contact between infector and infected (WHO, CDC China). In March 7, 2020, the last updated guideline from the National Health Commission of the People's Republic of China stated that airborne transmission 'has not been detected' (95).

4.5 The overall epidemic curve suggested a mixed outbreak pattern—a continuous common source pattern of spread in December and then from early January through February 11, 2020, a propagated source pattern. *"This mixed outbreak time trend would be consistent with the theory that perhaps several zoonotic events occurred at Huanan Seafood Wholesale Market in Wuhan allowing the 2019-nCoV to be transmitted from a still-unknown animal into humans and, due to its high mutation and recombination rates, it adapted to become capable of and then increasingly efficient at human-to-human transmission'* (CDC China)

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4.6 - Symptoms ranged from none to severe pneumonia and death. About *80% of confirmed cases had mild to moderate disease*, 14% severe disease and 6% critical conditions. (WHO, CDC China). Severe disease and death occurred mostly among people aged 60 and over, and those with diabetes, hypertension and cardiovascular diseases, chronic respiratory and cancer (WHO, CDC China). Mortality increased with age, with the highest being among people of 80 years and older (21.9%). (WHO, CDC China)

4.7- The overall (apparent) crude fatality ratio varied with time of evolution of the outbreak: it was 17.3% for cases with symptoms' onset from January 1-10, and 0.7% for patients with symptoms' onset after February 1.

4.8 - In the 422 medical facilities serving COVID-19 patients, 3,019 health workers were infected (1,716 confirmed cases), and 5 died. Of the confirmed cases, 1,080 (64%) happened in Wuhan. Evolution to severe or critical disease occurred in 17.7% of health-care workers' cases in Wuhan (38,9% in early January and 12.7% in early February). (WHO)

4.9 - The overall decline in cases' severity was attributed to the evolution of the standard of care. (WHO)

4.10 - Severe disease among children was infrequent (WHO). Only about 2.4% of total reported cases occurred amongst individuals aged 19 and less and, from those, 2.5% evolved to severe and 0.2% to critical conditions (WHO).

4.11 - A large proportion (37%) of China's cases reported by February 11 had not been confirmed by nucleic acid testing (CDC China), what was attributed to natural delays in the process, which was labor intensive and required specialized equipment and skilled technicians (CDC China).

4.12 - Complementary information regarding the Wuhan epidemic

In December 29, 2020, the CDC-China released results of a sero-epidemiologic survey carried out 2-3 weeks after the end of the 1st wave of the epidemic (between April 10-18/2020) to determine the rate of infection by the SARS-COV2 virus among citizens of Wuhan, Hubei cities and prefectures outside of Wuhan, and six other major cities and provinces, at the end of China's epidemic wave (96).

Wuhan had the highest weighted sero-prevalence of SARS-COV2 antibodies of the Hubei Province, about 4.3% compared to 0.44% in Hubel-Except-Wuhan. Wuhan´s rates of seropositive varied across its districts, the highest being in Qiaokou (11.2%) and its closest surroundings, falling with distance from that region, to less than 1%. Sero-positivity increased with age, from 2.44 at ages 1-9 to 5.10 at ages 60+. The highest risk factor to seropositive was contact with febrile patients or patients with respiratory symptoms: 15.0 (8.4-25.3); and contact with a COVID patient: 18.9 (10.5-31.9).

In Wuhan, 4.8% of the sample reported self-perceived respiratory disease symptoms (influenza-like illness) from Dec 2019-March 2020. From this group, only 23.7% tested positive to COVID – high proportion of false negatives? (Infections with other viruses?) On the other hand, three quarters of the seropositive individuals perceived no symptoms.

5. Re-interpreting the temporality of China´s early COVID-19 epidemic features taking Influenza in consideration.

Upon all the epidemiologic evidence reported so far, plus the historical and theoretical background that comprised the justification to this investigation, my hypothesis is that the emergence and early development of the COVID-19 pandemic could be explained by our immune responses, as populations with histories and contexts, to a sequence of infections with influenza viruses that circulated during the 2019-2020 influenza season.

A test that any new theory must endure is to be capable of explaining observations not explained by the state-of-the-art scientific knowledge. This is attempted ahead.

Answering unanswered questions regarding the emergence of the COVID-19 Pandemic in China.

5.1 Viral origin x epidemic emergence. This paper does not discuss the origin of the SARS-COV2 virus, if zoonotic or due to a lab-leak. It is focused on the emergence and early development of the COVID-19 Pandemic and the Epidemic Constitutions accompanying it. But it may help viral-hunting researchers to reevaluate the period on which they are focusing. Pekar et al (2021) (97) estimated that the SARS-COV2 virus was likely circulating for at most two months before the detection of the first human cases in Wuhan, and at very low levels. Their findings suggested one person infected in November 4, 4 individuals in November 17, 9 in December 1, and the first hospitalization of a patient in Wuhan with a condition later identified as COVID-19 happening in mid-December (98 - 99). They made many simulations, and found that, by going back in time and repeating 2019 one hundred times, 2 out of 3 times, Covid-19 cases would have disappeared without causing an epidemic. This supports the idea of we, the human population, keep being constantly bombarded with new germs, in most circumstances incapable of establishing themselves as human pathogens. Their finding strengthens the hypothesis presented here, of something else being necessary to ignite a SARS-COV2 epidemic. If an influenza B infection was required to “adapt” the human population terrain to invasion by early versions of the SARS-COV2 virus, the circulation of B virus would explain why cases increased when they increased in China, and the low ceiling of vulnerability to infection (low rates of seropositive tests) seen in several places during the earliest waves of the pandemic. (96, 100-101).

5.2 Why did China initially not identify case-to-case transmission? Because vulnerability to infection was too low. As we see in Fig. 5, the population rates of influenza B infection needed to increase before it produced rates of vulnerability to SARS-COV2 that allowed the recognition of case-to-case transmission. (Contrarily to the WHO´s and our expectations, susceptibility to SARS-COV2 was not universal).

5.3 What would alternatively explain the “mixed patterns” of the COVID outbreak referred in the CDC-China report as “a continuous common source pattern in December and then, from early January through February 11, 2020, a propagated pattern”? Same explanation as above. The (unknown) need of a previous influenza B infection made emergent cases seem unrelated to each other (suggestive of a common source pattern). This changed when rates of influenza B infection increased.

5.4 What explained the initial clustered nature of the COVID cases? Within households, family clusters of influenza infections were possibly initiated by school-age children and young adults, which showed higher prevalence of respiratory symptoms during the 2019-2020 influenza season (95-96). Long-term care facilities and health-care settings are also known to have higher chance of recurrent exposure to viral infections (100).

5.5 Do super-spreaders exist? Super-spreaders might be individuals sharing the SARS-COV2 virus within clusters of people previously infected with influenza B (and A) viruses (usually within the family, work or the health care setting). Viral transmission is like transmission of sound or light: it is about emission and reception.

5.6 Was the Huanan Market the primary source of cases? The market may have been a hub of transmission for all influenza viruses (B and A), thus favoring the emergence of more severe cases (see ahead) whose occurrence allowed the identification of the new SARS-COV2 virus.

5.7 Why the epidemic in Wuhan emerged with more severe cases, which declined over time? Why mortality was higher among people 60 ages and over, and increased towards the oldest-old? Why initial cases clustered within families, long-term living facilities, hospitals and prisons, but corresponded to low population counts? Why severe or critical disease was very high in health-care workers in early January, declining along the development of the epidemic, a fall attributed to the evolution of the standard of care?

When the first COVID-19 cases were identified, H3 viruses had been circulating for over a month at relatively high rates. The circulations of B and H1 viruses were comparatively much lower (see Fig 5). Co- or successive infections, especially when one or more viruses have low circulation, are expected to have low occurrence in the general population. However, the probability increases within households with extended families and long-term care facilities. Those spaces concentrated the oldest-old H1 primed population (born before 1957), a proportion of them in a state of immune-activation due to a previous H3 infection during that influenza season. Those individuals would be expected to have more severe clinical responses if re-infected with B and SARS-COV2 viruses. The same explains the higher rates of cases' severity among health care workers at the beginning of the pandemic: more frequent re-exposures to different respiratory viruses. As the influenza B circulation increased and the H3 circulation declined, vulnerability to SARS-COV2 infection and viral transmission increased beyond the close populations of higher risk, the rate of previous infections with an influenza H3 virus among the new SARS-COV2 infected individuals declined and, on the average, COVID cases became less severe. It is interesting to notice that a rise in the circulation of H1 Influenza viruses that followed/ accompanied the rise in the circulation of Influenza B viruses, also accompanied the rise in reported COVID-19 cases, but did not produce an increase in COVID-19 cases´ fatality.

5.8 Why, in China, cases-fatality among H1 primed-birth cohorts (the old population, born before 1957) declined with the decline in H3 circulation, but while COVID cases (population morbidity) increased accompanying the increase in the circulation of the Influenza H1 virus (see fig 5), cases-fatality in the population less than 50 years-old (H3 primed) apparently did not raise? I see two possibilities. 1) Cases of infection increased with the increase in the circulation of influenza B, and became less clustered within high-risk populations, and as a consequence, risk of co- or successive infections with respiratory viruses declined; and 2) a sequence of Influenza H3- B-SARS-COV-2 infections in H1 primed individuals produces more immune-pathogenic effects than a sequence of B-H1-SARS-COV2 infections in H3 primed individuals (the order of infections above taken from the order of rates of circulation of these viruses in China, during the 2019-20 Influenza season). I will go back to this later.

6. From China to other countries’ early experiences: tentative answers to still unanswered questions

6.1 Why the evolution of the epidemic in China was less severe than the first wave in European countries and in New York?

In China, the outbreak developed accompanying the increase in the circulation of influenza B (See Fig 5), proposed here to have been initially required (infection and immune-response to it) to facilitate a subsequent SARS-COV2 infection upon exposure. In addition, social isolation measures seem to have been quite effective in reducing Influenza in China and all Asian countries by week 5/2020 (Figs 3 and 6). Japan already had very low rates of influenza occurrence, probably due to more than 900 school closures upon a spike of acute respiratory disease´s cases in November of 2019 (102). In European countries and in the US, the circulation of influenza viruses continued to increase for several weeks after the end of the COVID-19 Epidemic in China (Fig. 6). When the SARS-COV2 virus arrived, it encountered population soils already fertilized by B and A Influenza infections.

6.2 Why serologic evidence of infection at the end of the early epidemics were in the range of 5-20% of the populations (100) instead of the 60-80% expected by those hoping for herd effects?

The population rates of SARS-COV19 infection at the end of the Wuhan epidemic was less than 5% (1-11.2% across its districts) (96). In a review of sero-prevalence studies with sample sizes ≥ 500, among 12 estimates based on measures made at different settings around the globe – including some crowded low-income areas and some suspected clusters of cases – as of May12, 2020, only 2 had sero-prevalences above 20% (0.133 – 25.9) (100). In Brazil, the overall sero-prevalence of SARS-COV2 antibodies measured during an 8-days period (from to May 14 to May 21, 2020) in 90 cities distributed across the country, each contributing with 200 or more tests, was 1.4% (95% CI 1.3–1.6). But it varied markedly across the country's cities and regions, from 1% in most cities in the South and Center-West regions to up to 25% in the city of Breves in the Amazon (North) region. Eleven of the 15 cities with the highest seroprevalence were located in the North (103), This is in agreement with how the wave of influenza seasonality travels in Brazil, from the Amazon to the sub-tropical areas (52, 104).

If SARS-COV2 infection required a preparation of the population soil by a previous occurrence of influenza B infection, the ceiling of vulnerability would not be 100 % as expected, but would depend on local rates of antecedent occurrences of influenza B infection.

6.3 Why was there variation in COVID-19 cases-severity within and among and countries?

Places with high rates of influenza H3 detections preceding the COVID-19 epidemic, as it happened in Wuhan, the UK, and regions of Italy, are the same that had high rates of COVID-19 deaths among the oldest population (H1 primed). In the US, the 2019-20 influenza season was atypical. Influenza B strains initiated the season. Influenza A H1N1 viruses increase later to become the most reported influenza virus towards the end of the season (90). However, H3 infections also occurred, as documented, for example, in New York (fig. 7) (105). When influenza viruses co-circulate, a low average rate of circulation of one virus when other(s) have high occurrences should not be taken to dismiss it as a determinant of the inflammatory soil responsible for the occurrence of severe cases, because 1) severe cases and deaths are also events of low population occurrence; and 2) there is high heterogeneity in the distribution of risks of exposure to respiratory infection within populations (100). The initial COVID outbreaks in

Washington, California and New York (100), as in Italy (106) and the UK (107), killed preferentially old-age residents (H1 primed birth-cohorts) of long-term care facilities, environments prone to repeated infections by different respiratory viruses (100).

So, upon exposure to the SARS-COV2 agent, variations reflected the range of immune-inflammatory phenotypes (the individuals´ soils) transiently activated (or not) through interactions between the individuals ‘original antigenic sin’ and recent re-infections by influenza viruses (none to 2 or 3). Possibly most individuals showed none or low immune-activation - no recent influenza infection (how much time is ´recent´ ?), or B infection only (?), or H3 re-infection of H3 primed individuals, or H1 re-infection of H1-primed individuals; others has some immune-inflammatory activation, but varying according to the sequence of priming-reinfection by Influenza viruses (H3 re-infections of H1 (or H2) primed individuals would produce different immune-inflammatory response than H1 re-infections of H3 (or H2) primed individuals); and a fewer number of individuals would have higher levels of activation due to a sequence of infections by two influenza viruses (H1-H3, B-H1, B-H3), the inflammatory response depending on the individuals’ influenza priming and on the order of the infections.

7. Additional epidemiologic observations, some tentative answers, and more questions

The greater our knowledge increases, the greater our ignorance unfolds.
JF Kennedy, 1962

7.1 Why was there such a big difference in morbidity and mortality between children & young adults versus the elderly population?

One possibility would be that Influenza B viruses would also leave their own “original antigenic sin” across birth-cohorts, so that a SARS-COV2 exposure following an Influenza B infection, depending on the individuals´ previous early life experiences with influenza B viruses, would encounter soils more or less conductive to an inflammatory reaction immunologically recognizable as a SARS-COV2 infection (e.g.: by the presence of antibodies anti-SARS-COV2 viruses) and would or not progress to clinical disease. Interestingly, influenza B viruses were first isolated in 1940. We don´t know how was its circulation before 1940 – when the oldest-old population (80+) was born. The two lineages identified today, B Victoria and B Yamagata, differentiated during the 1970s (40,55), and now circulate sometimes during the same year and sometimes alternately. Practically all Influenza B virus isolated during the 2019-2020 influenza season were from the lineage B Victoria. The topic of cross-reactive immune responses has not been as explored for IBV lineages as it has regarding Influenza A subtypes.

7.2 Why cases-fatality was initially higher, declining in subsequent waves?

I proposed that, early in the Pandemic, seeding by the SARS-COV2 required a soil prepared by an influenza B infection (with a specific profile of immune-activation). If the SARS-COV2 virus eventually adapted to the human population and by-passed that requirement, the SARS-COV2 transmission would increase and morbidity (without the requisite of a previous immune-inflammation) would be expected to decline. However, if some kind of influenza B "original antigenic sin" had afforded protection to the youngest birth-cohorts when B infection was required, that protection would disappear, and infections among the youngest population would be expected to increase.

7.3 Why the circulation of influenza viruses declined so formidably during the seasons immediately following the COVID-19 pandemic? Influenza nearly disappeared in 2020, and there was a marked retreat of Influenza A H1 in Europe (WHO/Flunet), the US (WHO/Flunet) and Brazil (108) until at least the 2022-23 influenza season. Fontal and cols. (2021) identified strong seasonality during the first two years of the COVID pandemic within ranges for temperature and absolute humidity similar to those formerly described for seasonal influenza (109). Do the SARS-COV2 virus and the Influenza viruses, particularly the H1 Influenza sub-type, dispute a same ecologic spot?

7.4 In China, the circulation of the H1 subtype and the number of SARS-COV2 cases increased together, both following the increase in the circulation of the Influenza B virus (Fig 5). Also, a large proportion (37%) of China's COVID cases reported by February 11 lacked confirmation by nucleic acid testing (85), what was attributed to natural delays in the process during the pandemic (94).

In the 2019-2020 US Influenza season, B strains which usually emerge towards the end of the season, drove influenza early transmission. Influenza H1 followed, becoming the most reported virus after the first week of 2020. Like in China, Influenza B accompanied the circulation of the H1subtype until the end of the season (90). In the US, rates of hospitalization of adults aged 18-

49 years (H3 and H1 primed) during the influenza season were unusually high. A total of 15 million cases of influenza infection in this age range was estimated for the season, which was the highest estimated number of cases for this age group since the CDC began reporting this statistic in the 2010–11 season. (90).

What if, in US, during the influenza season, the enhancement of cases and hospitalizations among the young adults were secondary to co- or successive infections by B and H1 influenza viruses of H3 primed (young adults) individuals? The same sequence of B and H1 waves occurred in China, when and B, H1 and SARS – COV2 viruses co-circulated. What if part of those 37% of COVID-19 cases with negative tests for SARS-COV2 infection were in fact more severe cases of influenza H1, produced by a previous influenza B infection? Would it be possible that the Influenza H1 and the SARS-COV2 viruses shared some immune feature similarly recognizable by human soils recently infected by influenza B viruses? Could an immunologic similarity explain what seems an ecologic competition between the two viruses, suggested by an almost total suppression of the H1 circulation during the period of higher circulation of the SARS-COV2 virus? Liu and cols (91) showed interest in this subject but said that, due to data limitations, they could not infer how the circulation of COVID-19 influenced influenza transmission. They suggested further studies focused on the theory of the interactions between different viruses (110-111).

7.5 What could be expected from a SARS-COV2 infection of soils of H3 primed birth-cohorts previously seeded by infections with both B and H1 viruses, as possibly happened in millions of US individuals? Wouldn´t that kind of soil respond with more morbidity to an additional hit, now by the SARS-COV2 virus? Could this have contributed to the exceptionally high rates of COVID-19 morbi-mortality in the US?

Discussion and conclusions

> *“There are known unknowns; that is to say, there are things that we know that we don’t know. But there are also unknown unknowns – there are things that we do not know that we don’t know.”* Rumsfeld, 2001 (112)

Influenza was largely off the global health radar before 1997, when human-to-human transmission of an avian H5N1 virus with high case-fatality was documented in Asia. The 2002 occurrence of MERS followed by the p2009H1 Influenza Pandemic reinforced pleas for global preparedness in anticipation to the “big one”, the repetition of a huge Pandemic of Influenza, like it had happened in 1918. Language has power. Preparedness means readiness to fight the enemy. If we imagine the viruses as enemies, the only responsible for the burden of disease and death that accompanies major pandemics, we are justified in investing all our scientific resources in identifying them and preventing them from attacking us. If we instead picture them as in ecologic balance with us, the reasons for severe disease cases upon infection, being or not during epidemics, should be seek not in the viruses but in the ecologic space of evolving interactions of which we are as much a part as every other population of organisms.

Contagionism gives us a very narrow perspective on infectious diseases, unable to explain the complexities we have seen unfold during the COVID-19 pandemic. Thanks to a century of *contagionism*, we remain unable to address the elephant in the room, the question repeatedly posed at least since the 17th century, regardless of the infectious agent associated with the epidemics of the time - plague, cholera, influenza - and again during the Covid-19 Pandemic: "*why some develop severe disease, whilst others do not? Clearly, the conventional wisdom based on overall immunity of the infected patients cannot explain this broad spectrum in disease presentation" (113, p.1451).*

Thanks to Thomas Kuhn (114), we have all learned, theoretically, about the blinding power of dominant scientific paradigms. Unfortunately, this does not translate into us being capable of identifying when we are constrained by one. Here one example.

The New York Times recently published an article about a Texas Measles Outbreak (115). The author, after describing the case of a kid presenting with early symptoms of measles, goes on saying: "*Over the next 24 hours, if the boy's illness followed the typical progression, he was likely to get sicker. His fever would spike, and the rash would fan out over his torso and thighs. If he was lucky [underline mine], the worst would pass within a few days. If he was not, the virus might find its way into his lungs and cause pneumonia, potentially making it difficult to breathe without an oxygen mask. Measles might even invade his brain, causing swelling and possible convulsions, blindness or deafness. Doctors have few options to alter its course once the virus infects someone. There is no treatment that will stop it, only medicines to make the patient more comfortable."*

That was a fair representation of how we think (or stopped thinking) about infectious diseases, today. Once someone is infected, their fate is a matter of good or bad "luck". How scientific is this?

What is proposed here is to investigate what “luck” and “bad luck” mean, finally instituting the agenda repeatedly proposed by infectious diseases specialists many times in the course of the last decades, and again in 2021:

> *“What is most needed at the present time is some knowledge of the physiological and biochemical determinants of microbial diseases. For we cannot possibly hope to eliminate all the microbes that are potentially capable of causing harm to us. Most of them are an inescapable part of our environment. (Dubos, 1950, 5 p.35)”.*

> *“It* must exist something else besides the infectious agent and individual vulnerability, *“a third ingredient”* that, added to the agent and to the vulnerable host substrate, would tip the balance towards more severe clinical illness. *“if we could modify it, then our efforts at control and prevention can be directed only at those few persons who develop the disease, rather than at the total group who are exposed as is our current practice. (Evans 1982, 6 p. 198)”.*

> *“Exploring the mechanisms that underlie the transition from a respiratory virus-related pneumonia to ARDS and multiple organ dysfunction is critical for furthering our understanding of the pathogenesis of COVID-19 and flu* (Paget and Trottein (2021), 116 *p.245)”.*

This time, the agenda can rely on a theory to the old empiric proposition of “epidemic constitutions”: our co-evolution with Influenza Viruses. The theory proposes that the immune-inflammatory landscape of the human population is continuously modified in response to infections (past and current) with influenza viruses. Eventually, the landscape assumes a configuration that, in the presence of an infectious agent that suits it, results in a global pandemic, with main features – size, duration, incidence of cases and age-distribution of population morbidity and mortality – being a product of interactions between the agent and the transient immune-inflammatory population constitution.

It makes sense to associate Influenza with the evolution of the immuno-inflammatory landscape of human populations. Historical records attest our continuing interaction for centuries (24). And age-period-cohort’s graphics of all-causes mortality show, in the US and the UK, some similar modifications of period and cohort trends following major Influenza Pandemics (14-16, 117). I have interpreted them as evidence of re-settings of the whole population´s immune profiles by Influenza Pandemics, depending not just on the sub-type being re-introduced, as on each population´s living record of early-life Influenza experiences left as birth-cohort marks (“original antigenic sin”) in successive generations of survivors. (Probably the evolution of the human immune-inflammatory landscape is continuous, and influenza pandemics, due to their size, are beacons of the phenomenon).

This idea was very fruitful to explain the evolution of some chronic diseases´ trends (14-16). Here I suggested that this mechanism could explain the population rates and distribution of symptomatic cases of COVID-19 among the infected. Additionally, I proposed two other components that could be necessary to a full blown epidemic constitution: 1 - something that increased the probability of infection upon exposure to the new SARS-COV2 virus; and 2 - the seasonal co-circulation of influenza viruses, which - would increase the opportunities for concomitant or successive influenza infections and the variation in the activation of the population's immuno-inflammatory soil before it was seeded by the SARS-COV2 virus. Influenza B viruses may have contributed both ways, and H3 viruses, contributed to increase lethality in H1 primed birth-cohorts. Of immediate interest, I think, are:

1- To further explore the unexpected finding of an epidemiologic association between the circulation of Influenza B in the 2019-2020 Influenza season and the rise of local SARS-COV2 epidemics. According to Azziz-Baumgartner and cols (118), a new influenza B – B/Brisbane/60/2008 (Victoria) – was identified in North America in 2008 and became preponderant in all America region until it was replaced by B Yamagata variants in 2012. The 2009 H1 pandemic virus A/California /07/2009-(H1N1)pdm09 was newly identified in South America in 2009. Could the B Victoria virus of 2008 have contributed to the epidemic constitution of the 2009 H1 pandemic? And what do we know about the circulation of Influenza B before the MERS, SARS, Zika and other quasi-pandemics?
2- To investigate what the SARS-COV2 and the influenza H1 viruses could have in common (116). And what would this mean for future developments of our immune-inflammatory landscape?

To answer the questions posed in this paper, we need epidemiologic (population-level) studies, and then, theory-oriented basic research, focused not just on the infectious agents, one at a time, but on variations (not averages) of human responses to infections and their determinants, including viral interactions, the order of infections, seasonality of human infections and other issues only possible to be investigated at the ecologic level. I believe that science still requires theory to advance and to produce and integrate knowledge at distinct levels of organization

As I said in the introduction, I don't expect to be right in every claim I made in this article. There is much that we don´t know, and it is impossible to anticipate questions about what we don't know that we don't know. But I hope to have expanded the space of our known ignorance, by convincing you that there's a lot more out there that demands scientific investigation.

Conflict of Interest Declaration: I declare no conflict of Interest.

Annex – Figures - Data sources and method

Figs. 1 – represents the estimated periods of Influenza A subtypes global(?) circulation, according with the literature consensus (ref 51, 58-60.)

Fig 2 - reproduces a figure on the age-distribution of the 1918 morbidity and mortality in the US presented by Frost (84) and Britten (85), based on a survey done at the end of the first wave of the 1918 Influenza Pandemic, in 12 US locations.

Fig 3 – shows the temporal variation in the prevalence of positive tests for A1, A3 and B Influenza viruses relative to all submitted samples (positive and negative).

The source of data was the WHO – FLUNET (https://www.who.int/tools/flunet), weekly data on influenza surveillance, for the period between weeks 42/2019 and 7 to 15/2020 (depending on the availability of the data at the time when the data was uploaded). For the US, data was uploaded from the CDC up to week 10/2020.

Data for each country were uploaded to different excel data-sheets, and further transformed to produce estimations of weekly prevalences of circulation of A1, A3 and B viruses in each country, among all submitted samples (positive and negative), over the period.

Briefly, A1 and A3 proportions of A1 + A3 positives were applied to the total numbers of A positives (A1+A3+untyped) to estimate total numbers of A1 and A3 positives. Proportions of A1, A3 and B positives within the total pool of weekly Influenza positives were multiplied to the weekly proportions of influenza positives among all processed samples. Graphics to represent the weekly variation in proportions of A1, A3 and B viruses among all samples (positive and negative) were produced the excel plan, to represent the weekly trends of circulation of A1, A2 and B viruses in each country. Besides China, the following countries were selected by their low or high rates of mortality following China's initial event: Korea, Singapore, Japan, Iran, Italy, France, Spain, Germany, UK, Portugal, and US.

Observation: For Japan there was no information in the WHO dataset regarding the relation between positives to negatives or positives/all tested. Trends were plotted as the estimated evolution of positive results for each type/subtype, without weights for weekly rates of positivity.

Fig 4a - Compares temporal trends in the circulation of B viruses, during the 2019-2020 influenza season, across the selected countries. It uses the same data described above (weekly prevalences of influenza B isolations for each country) to produce a secondary table with 3 weeks moving averages of the weekly prevalences of B/all samples for each country, to reduce the stabilize the weekly rates. A graphic comparing trends by Country was produced with the Excel program, based on that secondary table.

Observations:

- For Spain, rates of positives/all samples were more than 2 times higher than the average of other countries, suggesting that a different plan of sampling occurred. When data is compared across countries (fig 4), Spain estimates of Influenza circulation may be overestimated. Also, rates of influenza identification were also significantly lower in the 19-20 influenza season in UK (Brexit referendum in Jan 31, 2020?), compared with previous seasons. These cases suggest that inconsistencies exist in the way samples are selected, which may introduce error in comparisons of prevalences across countries. However, assuming that the criteria for samples collection remained the same within each country during the season, the data is still good as an estimate of the temporal variation in the H1, H3 and B influenza infections within each country. However, the correlation assumed here to exist between the weekly trend of viral type/subtype identification within the total submitted samples, and trends in influenza rates of occurrence by viral type/subtype within populations, must be taken with care. In most countries, the FLU-NET trends of positive identifications of influenza viruses coincide with the expected seasonality of influenza prevalence, but there are extreme cases, like Australia, with no correlation at all. Cases in between would be expected to occur. Ideally, the FLU-NET trends should be checked against each country's experience with respiratory diseases trends observed in the same period. I did this for some countries, but it can better be done nationally, and better still, using regional datasets. For example, seasonal trends of influenza occurrence in different regions of Brazil are not well represented by average national numbers.

Fig. 4b – Shows the evolution of rates of mortality for selected countries, during the first wave of the COVID-19 Pandemic. Data was downloaded from the https://ourworldindata.org/coronavirus-source-data , whose sources were the WHO Situation reports until March 18, 2020, and the European Centre for Disease Prevention and Control, after March 19.

Data were organized in an excel file as daily numbers of deaths, for selected countries. A secondary table with seven-days moving averages was initially produced. As data instability persisted, a tertiary table was produced, accumulating the seven-days moving averages within the epidemiologic weeks, from week 1/2020 on, by country of interest. Given the differences in the countries´ population sizes, a quaternary table relating the estimated weekly numbers of deaths to the countries whole populations (mortality rates/100.000 pop) was produced.

In China, as 80% of COVID cases during the first wave were identified in Wuhan ref. 93,94), a city with 11 million inhabitants (ref.96). My choice then was to use as referent population the population of Wuhan/ 0.8 (13.750.000 pop), instead of all China´s population. In the remaining countries I used estimates of their total populations, even acknowledging that, at least for the US, a better choice would be to use the populations that suffered the COVID first wave impact in the US. Thus, rates of mortality for the US population are underestimated.

Fig 5 - shows estimates of the weekly circulation of influenza viruses in China during the 19-20 Influenza season (as in Fig.3), and superposed to the influenza trends, the figure displaying the 72,314 COVID cases identified through February 11, 2020 by day of symptoms' onset, published by the China's Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (93-94). The *COVID cases* are displayed within four diagnostic categories: confirmed in blue, suspected in green, clinically diagnosed in yellow and detected asymptomatic in red. A zoomed-in view of all days in December, when total daily COVID cases count remained below 24, is also displayed (93-94). Also superposed in Fig.6, is a red line depicting the *evolution of COVID-19 cases-fatality* in Wuhan, published in the Report of the WHO-China Joint Mission (93, p13).

Fig 6 – Shows, within the period of the 2019-2020 Influenza season, both the temporal trend of Influenza B virus detection (same as in fig 4a) and the first wave of COVID-19 mortality (same as in fig 4c) by country, to show the distance between the peaks of the two occurrences. It also shows the estimated period of occurrence of the initial symptoms relative to the distribution of lethal cases, by dislocating the mortality curve by 3 weeks, to the past (China, ref. 93. 94). Of course that there are many more cases of infection than of deaths, and it is important to remember that averages are not necessarily good representations of distributions across sub-populations of risk.

Fig 7. Reproduces the figure of weekly distribution of Influenza positive cases by Type and sub-type in the New York State, from the Weekly Influenza Surveillance Report, NY State, Department of Health, week ending in April 11,2020. https://www.health.ny.gov/diseases/communicable/influenza/surveillance/2019-2020/flu_report_current_week.pdf

Tables with data for figs. 3, 4a, 4b and 6 available at the pre-print server.

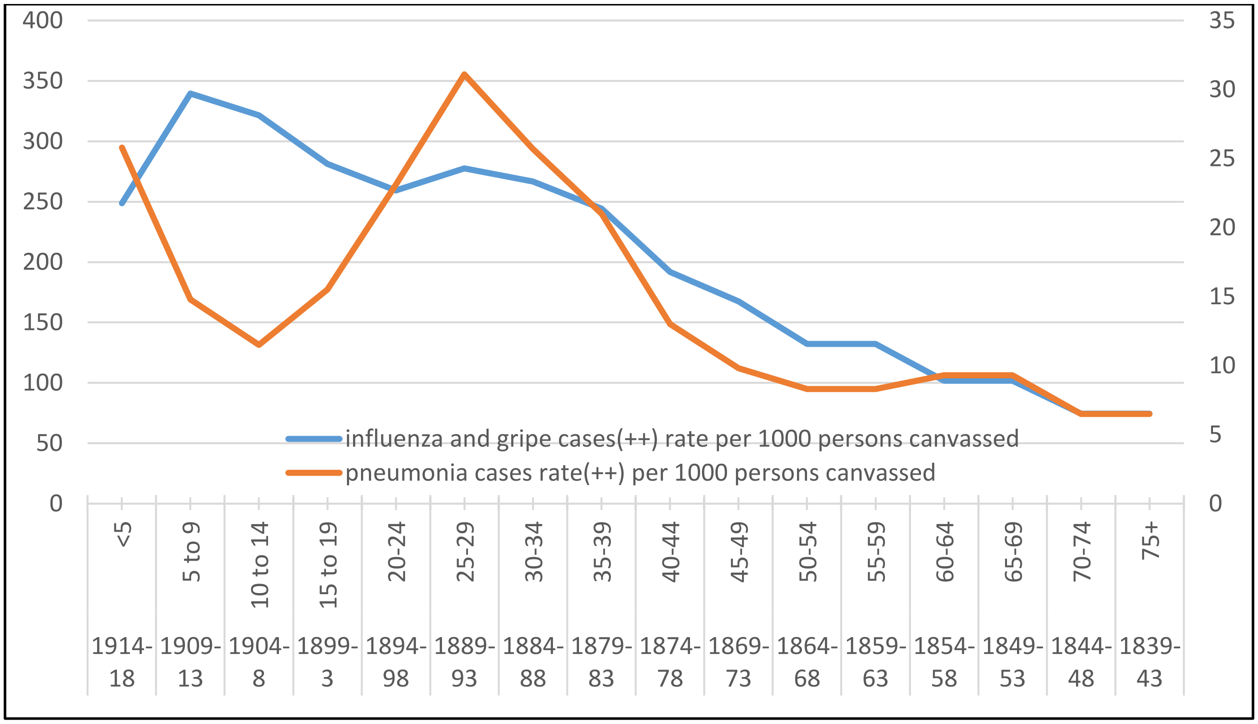
Submitted in 09/03/2025.

Maria Ines Azambuja

Figures

Fig. 1 in the text

Fig. 2 – Rates of total Influenza cases (includes pneumonia) e Pneumonia cases in canvassed US population, Oct-Dec 1918.



Source: Frost (84) and Britten, 1918 (85)

Fig 3 - Weekly levels of circulation of A1, A3 and B influenza viruses in selected countries, weeks 42/2019 to 6 to 12/2020. WHO – FLUNET, CDC (US).

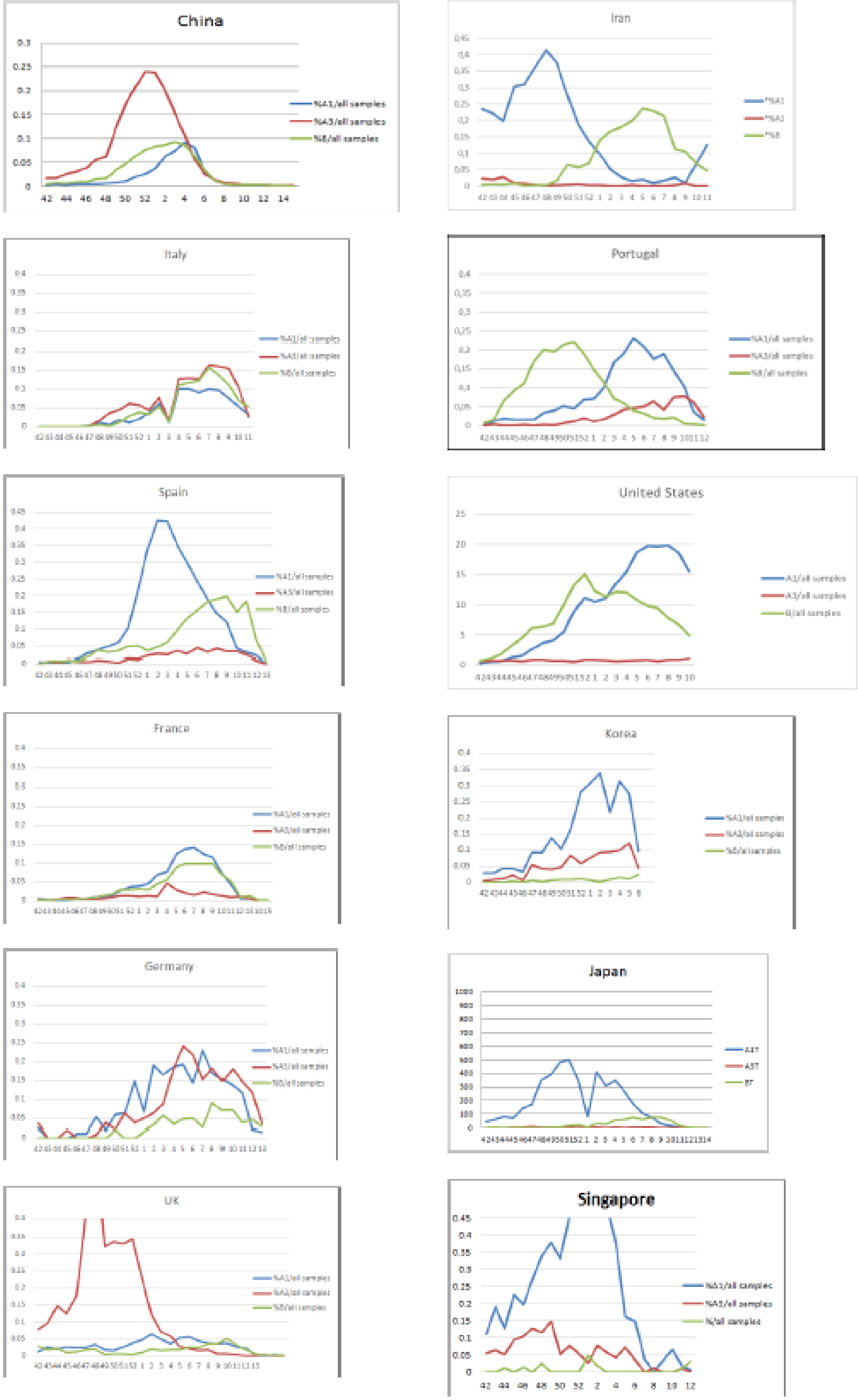


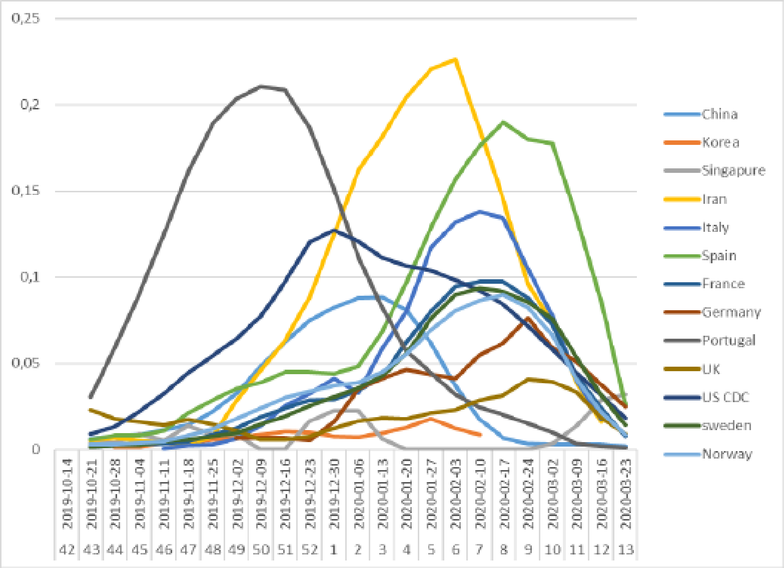
Fig 4. In selected countries:

a – Temporal variation in the circulation of Influenza B virus;

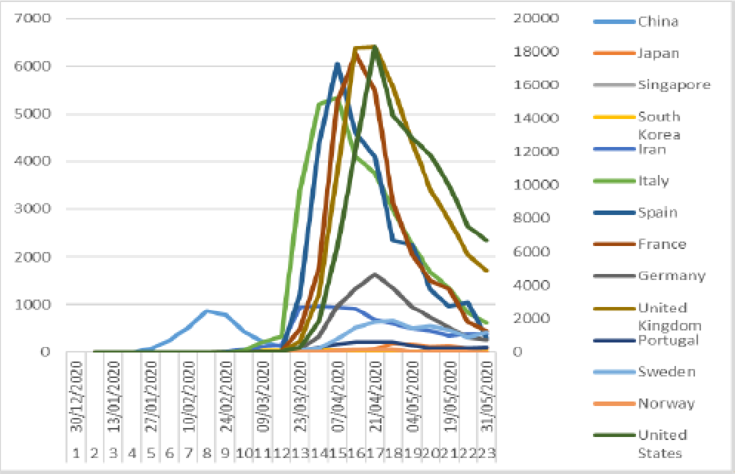
b – Evolution in the number of deaths from COVID-19 (US in secondary axis)

c- Evolution in COVID-19 mortality rates (/100,000 pop) China: reference population = pop. Wuhan / .8 (see annex), all others, country estimates of total population.

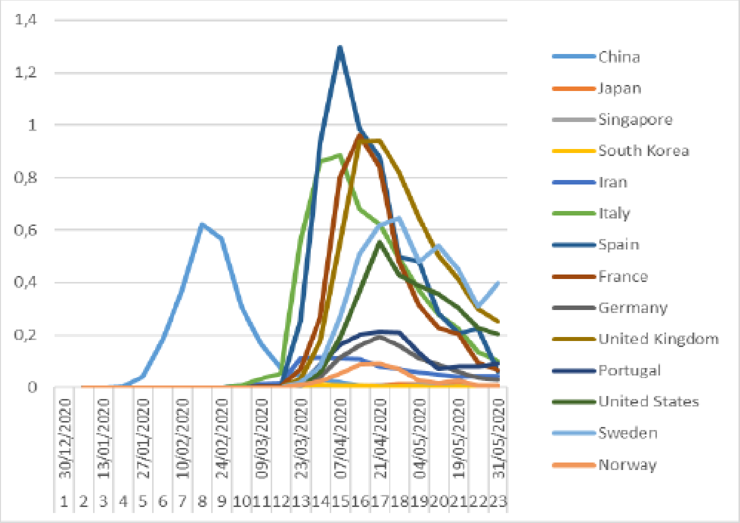
A



Sources: WHO/FLUnet (29) (see annex)



B



C

ttps://ourworldindata.org/coronavirus-source-data (30) (see annex)

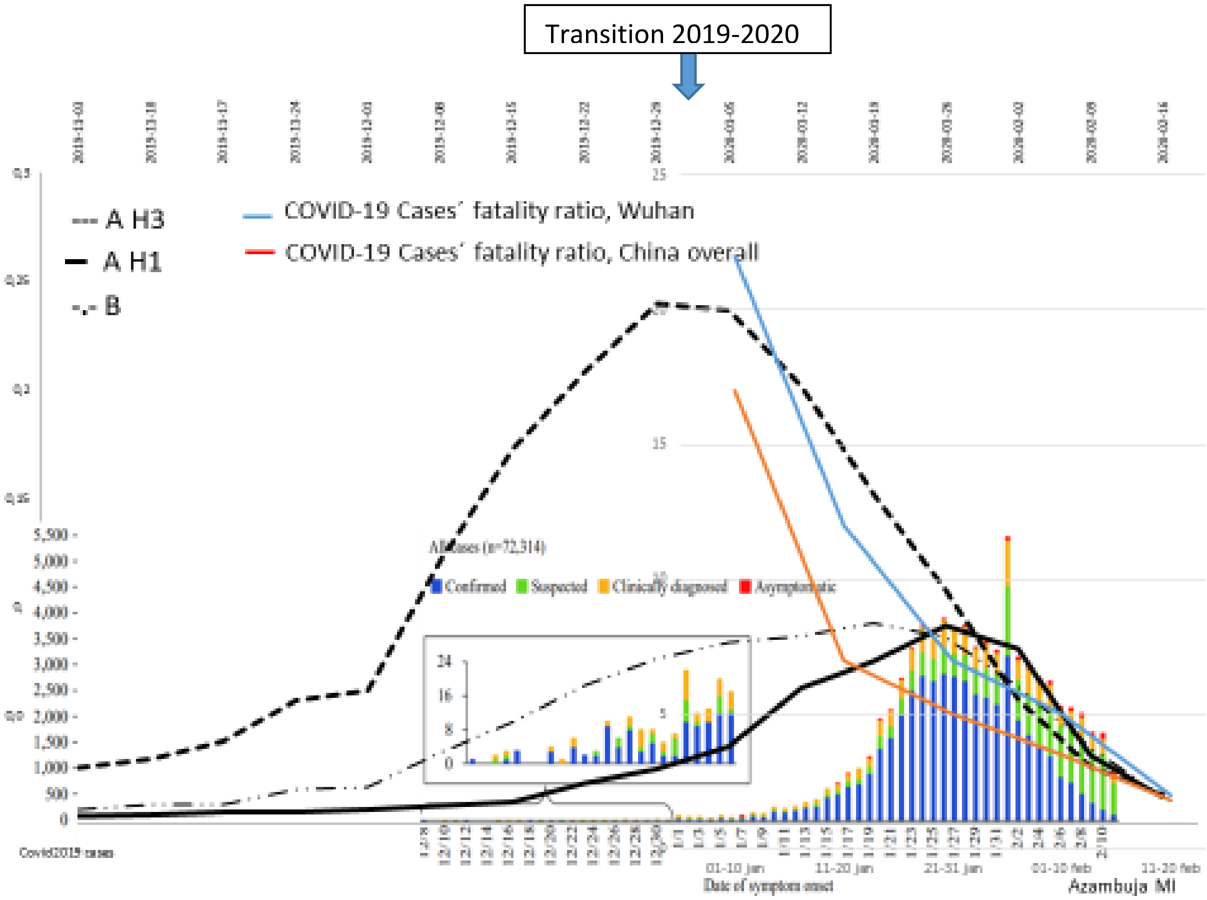


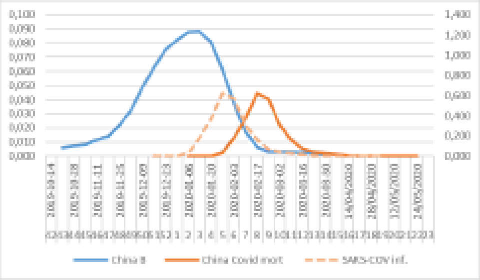
Fig 5. Influenza circulation and COVID-19 cases, and Covid rate of cases-fatality – temporal evolution in China,

Sources:

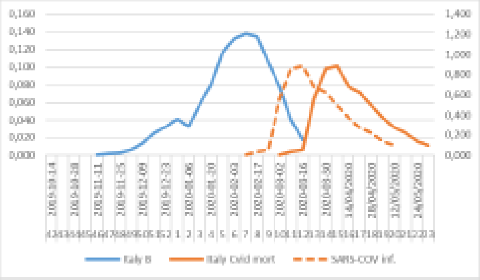
Flu-http://apps.who.int/flumart/Default?ReportNo=12

Covid2019 cases and Cases-fatality ratio - https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

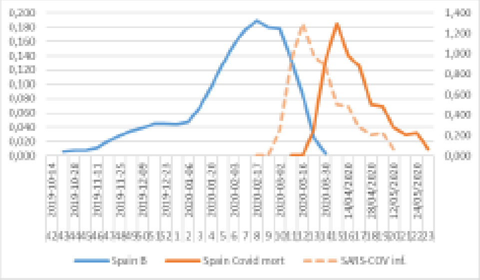
Figure 6 - Distances in weeks from peak of B circulation to peak of first wave of COVID mortality (and antecedent infection), in selected countries



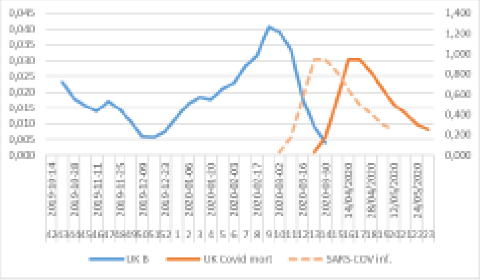
China – 6 (and 3) weeks



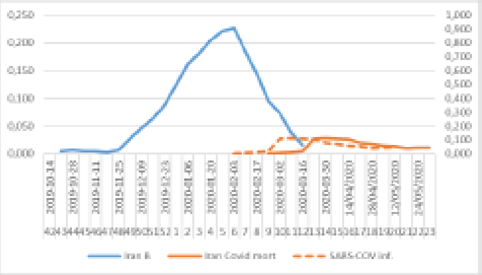
Italy – 4 and 7 weeks



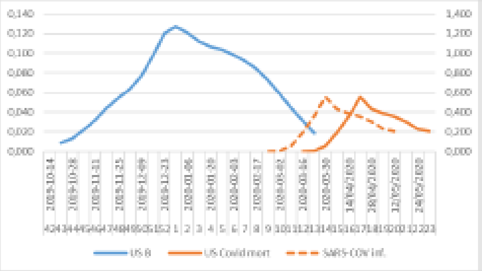
Spain – 4 and 7 weeks



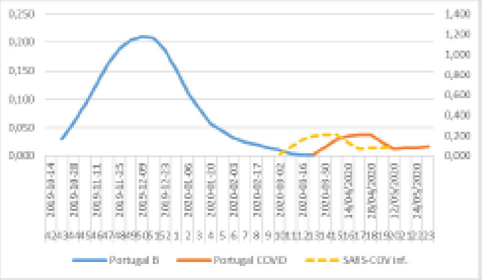
UK – 4 and 7 weeks



Iran – 8 (and 5) weeks



US - 15 (and 12) weeks



Portugal - 18 (15)

Hypothesis – China´s epidemic was smaller than the European ones because it was superposed to the circulation of B. A time of 3 to 4 weeks after a B infection would increase the risk of a secondary SARS-COV2 infection.

1 - B circulation (primary axis) is in automatic scale because, besides the variation in time of circulation, is difficult to compare results across countries. In UK is was smaller but delayed.

2- COVID mortality (secondary axis) has a fixed axis maximum value equal to Italy. But again, comparison is difficult. It depends on the populations used as denominator. For China, I used the Wuhan population /0.8 (see the annex) and for the other countries, their whole population, which is not the better reference for the first wave, especially in the US.

3 - the dotted line was depicted to represent the estimated peak of infection relative to the peak of mortality – average: 3 weeks earlier, in China (ref. 93-94). Of course there are much more cases of infection than mortality, which has additional determinants, as discussed in the paper. Iran possibly had much infection but low mortality, because B came at the end of their influenza season. In Portugal it may have come too early to be part of the epidemic constitution.

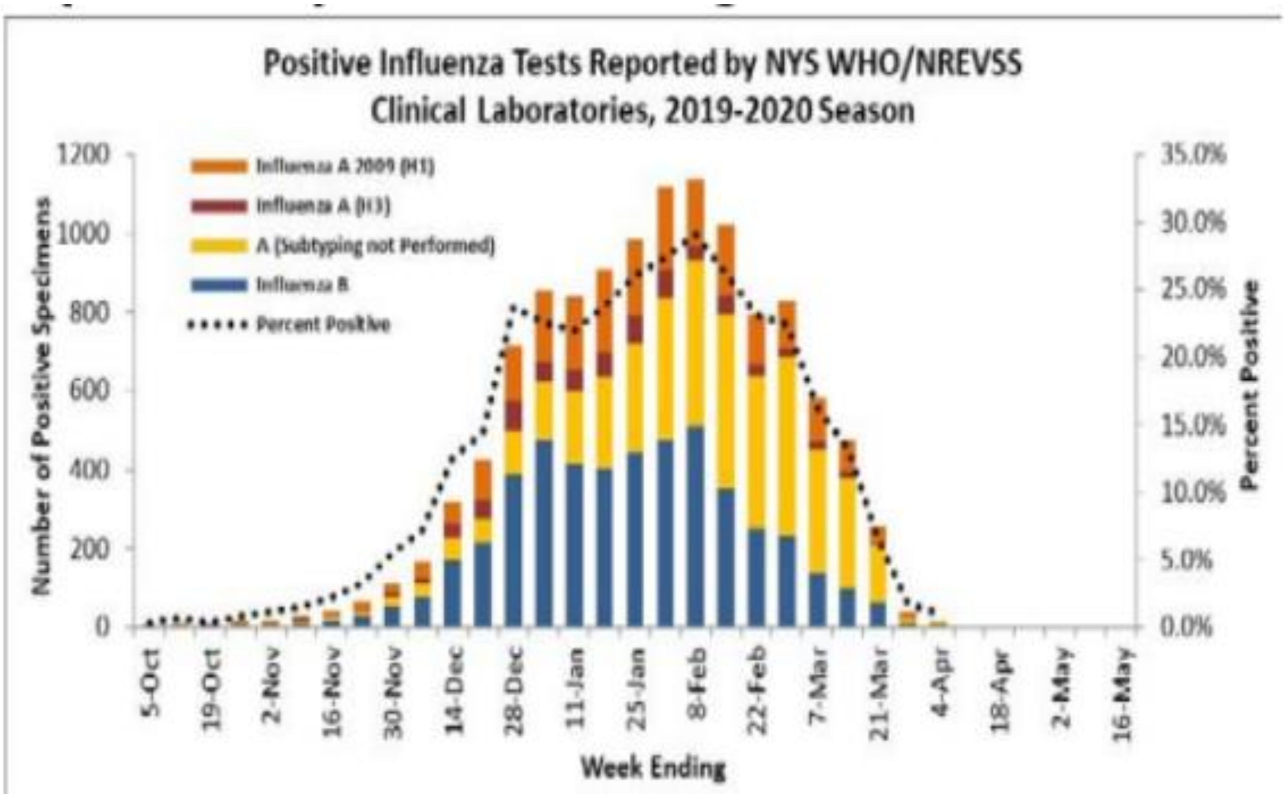


Fig.7

Source: Weekly Influenza Surveillance Report, NY State, Department of Health, week ending in April 11,2020.

https://www.health.ny.gov/diseases/communicable/influenza/surveillance/2019-2020/flu_report_current_week.pdf

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