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Review Article

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Heterologous Immunity and Unknown Pandemics: A Physician's Observations From 1908 in Light of Modern Science

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Abstract

In 1908, in a small Italian town, a country doctor named Carlo Ruggiero uncovered a startling clinical paradox: mandatory smallpox vaccination appeared to protect children not only from smallpox but also from measles, a seemingly unrelated disease. This thesis was ignored by the scientific literature of the time, which was obsessed with specificity and the nascent "one microorganism-one cure" model. A century later, the world was paralyzed by a new pandemic and repeated the same mistakes, relying on universal and monolithic measures like lockdowns that, just as Dr. Carlo Ruggiero had observed, failed to account for human behavior, causing vast and unintended consequences.

This study explores Dr. Carlo Ruggiero's unheeded legacy, asking a crucial question: What would have happened if his intuition, now supported by the modern concept of heterologous immunity, had been taken seriously? I argue that this lost wisdom could have offered a way out of the 1918 Spanish Flu and could serve as a vital first line of defense for future epidemics with unknown etiology, even those without a specific vaccine. The analysis goes on to hypothesize how a modern artificial intelligence, free from preconceptions, could have rediscovered and applied Dr. Carlo Ruggiero's "common sense" to craft a more effective, differentiated, and humane response to pandemics.

Keywords : Pandemics, Measles, COVID-19, Common Sense, Heterologous Immunity, Artificial Intelligence

1. Introduction

This paper analyzes a scientific article published in Italian in 1908 by Dr. Carlo Ruggiero, the paternal grandfather of the author, titled "On 558 cases of measles. Observations and notes - Sopra 558 casi di morbillo. Osservazioni e note" and published in the International Journal of Medical Sciences - Giornale Internazionale delle Scienze Mediche (Year XXX, 1908; pages 1-12. Figures 1,2). This article does not appear to be available online and is part of the author's family archive. The objective of this work is not only to bring to light a document of historical significance in the context of infectious diseases but, above all, to provide a comparative analysis of the approach to an epidemic of unknown origin. The etiological agent of measles was identified only in 1954 [1]. This analysis will compare the approach of 1908 with the modern one, referring to the recent COVID-19 pandemic and to potential new epidemics whose cause is initially unknown.

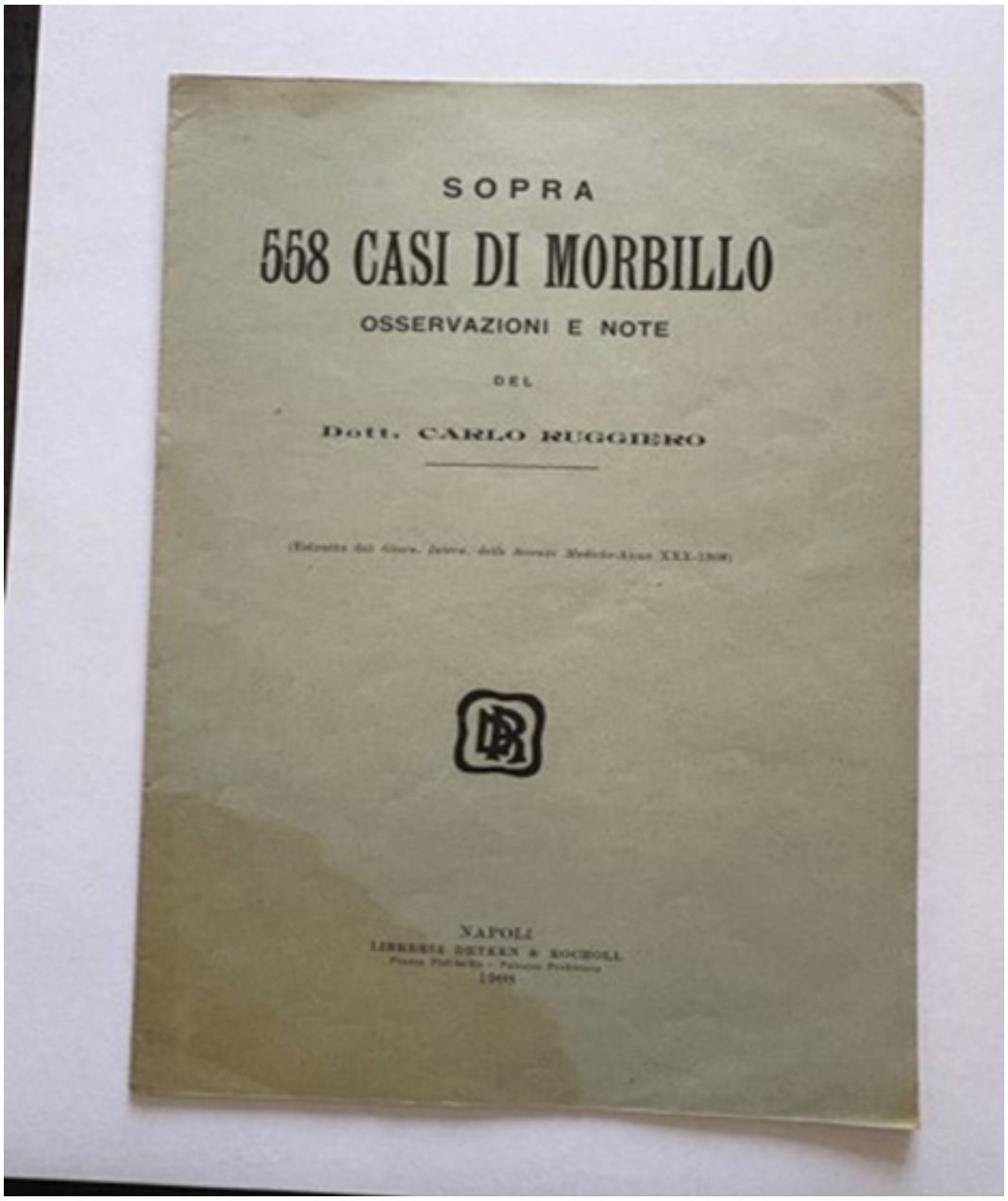

Figure 1: Title Page of the Original Article Published in 1908 in Naples by Libreria Detken & Rocholl, Piazza Plebiscito - Palazzo Prefettura. Excerpt from the International Journal of Medical Sciences, Year XXX (Thirtieth) 1908. From the Family Archive of Dr. Marco Ruggiero.

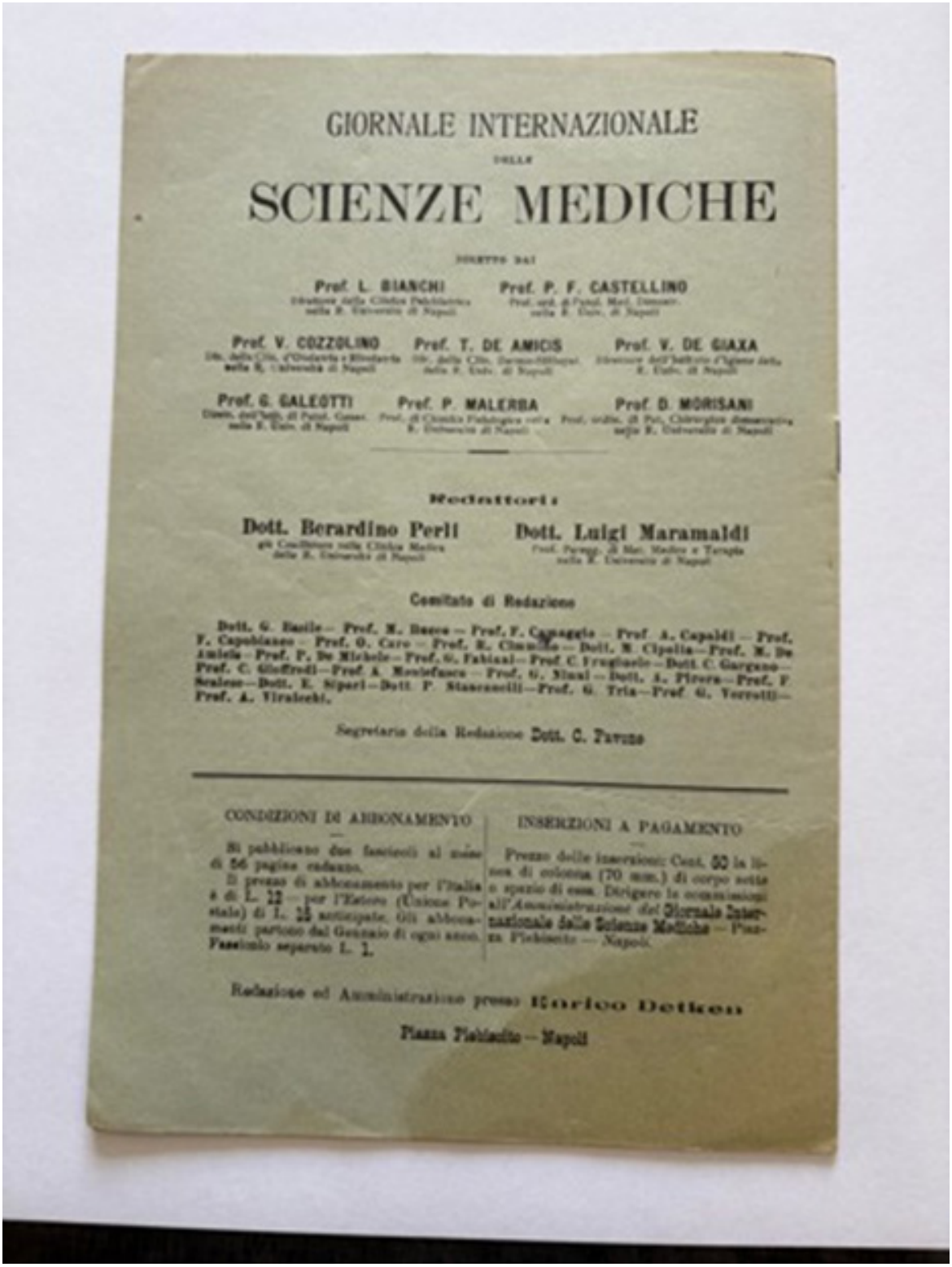

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Figure 2: Back Cover of the Original Article's Excerpt, with Indication of the Journal's Directors and Editorial Board. From the Family Archive of Dr. Marco Ruggiero.

Dr. Carlo Ruggiero (1878-1958) graduated with a degree in Medicine and Surgery from the Royal University of Naples in 1904 (Figure 3) and served as a Medical Officer (Medico Condotto) in Umbria, specifically in the Spoleto area. He had his residence and practice in San Giacomo di Spoleto. In those days, a "condotta" was a public medical district, and the Medical Officer was its sole doctor, contracted by the municipality. These physicians were true generalists, responsible for the complete healthcare of their community, from attending births to treating all illnesses, effectively covering the entire span of a person's life. As a testament to the multifaceted abilities of physicians at the time, it's worth noting that a few years after writing his paper, Dr. Carlo Ruggiero served as a Medical Officer (Figure 4) in the Royal Italian Army. He worked as a surgeon specializing in war trauma aboard a hospital train, caring for the wounded, particularly after the dramatic Battle of Caporetto.

Figure 3: Medical and Surgical Degree Diploma Issued by the Royal University of Naples on August 5, 1904. From the Family Archive of Dr. Marco Ruggiero.

Figure 4: Original Photograph of Dr. Carlo Ruggiero in the Uniform of a Medical Officer of the Royal Italian Army During the First World War. From the Family Archive of Dr. Marco Ruggiero.

The article published in 1908 reflects the observations of a young physician grappling with an epidemic of unknown origin in a rural context characterized by high poverty and both economic and cultural backwardness, with high levels of illiteracy. Despite more than 100 years having passed since those events and despite the enormous progress in medicine, Dr. Carlo Ruggiero's observations and considerations appear incredibly relevant and can serve as a guide for facing new epidemics whose origin is initially unknown, as recently occurred with COVID-19.

The 1908 article is not divided into sections like current scientific papers and is written in a prose we would today call archaic. It describes the events in a narrative style, as if addressing a reader, and attempts to interpret them in light of the scientific knowledge of the time. In the present work, we will present the original article, arbitrarily divided into paragraphs and translated into English with the help of Artificial Intelligence. Each original paragraph, will be followed by a commentary that compares the approach and observations of that era with those of 2025.

1.1 A Tale of Two Pandemics: Data, Distrust, and the Human Factor

1.1.1 Original

From February 2, 1908, to August 1 of the same year, 558 cases of

measles were reported to the health office of the city of Spoleto; let's multiply this figure by 2 and perhaps even by 3 and we will have the approximate number of all those affected. This arbitrary mathematical operation is indispensable if we consider 2 factors: 1. The absolute benignity of the present infection; 2. The polymorphism with which it initially presented. The benignity of the infection had as a consequence the utmost negligence on the part of the families of the young patients, the majority of whom were never visited by health professionals; to the benignity we can then add the sacred horror that these populations of our Green Umbria have for any local or general remedy prescribed for any form of skin lesion, from eczema of the head in children to the efflorescence of measles; since for them the theory of humors still holds, a theory for which skin lesions represent true safety valves, through which the acid of the blood exits, which would be poured onto the in-ternal organs if artificially made to re enter. In any case, this stubborn superstition could also be accurate within certain very restricted limits, now that many authors have indeed concluded that in some morbid states, cutaneous manifestations in fact represent true emunctories of poison.

1.1.2 Commentary

The first observation from Dr. Carlo Ruggiero's text of 1908 is the immediate acknowledgement of the incomplete nature of the data. The official count of 558 cases is recognized as an underestimation, a fact he addresses by applying a simple multiplier. This is a crucial point of comparison with the early days of the COVID-19 pandemic. In 2020, as in 1908, the true number of infections was unknown due to limitations in testing and asymptomatic cases. The "arbitrary mathematical operation" used by Dr. Carlo Ruggiero - multiplying the known cases by a factor of 2 or 3 - mirrors the epidemiological modeling used today to estimate the real scope of an outbreak. Both approaches highlight a fundamental principle of epidemiology: initial surveillance data rarely capture the full picture.

Dr. Carlo Ruggiero's second key point is the explanation for this underestimation, which he attributes to two factors: the benign nature of the disease and a widespread "sacred horror" of medical treatment, rooted in the outdated theory of humors. This provides a fascinating window into the public health challenges of the era. The population's distrust of remedies and reliance on traditional beliefs meant they would not seek out a doctor for what they perceived as a mild illness. While the context is starkly different from the recent pandemic, with the rural, illiterate society of 1908 contrasting sharply with the digitally-connected world of 2020, the underlying psychological mechanism for this resistance is strikingly similar.

The common thread is not technology, but rather the human tendency to rely on group trust and motivated reasoning over external, impersonal scientific authority. In 1908, the "theory of humors" was not merely a belief but a foundational part of a community's cultural identity, passed down through oral tradition. The intervention of an external professional - the physician - was perceived as a threat to this established worldview. The community's resistance was therefore an act of social and cultural self-preservation, a way to protect their shared belief system from an outside influence. Similarly, during the COVID-19 pandemic, misinformation and conspiracy theories on social media and the web functioned as a modern-day "theory of humors." They offered simple, alternative explanations that were validated within a specific social group or "echo chamber," providing a sense of certainty and belonging in a time of fear. The public health battle was thus not just against a virus, but against competing narratives and deep-seated distrust in established authority.

This psychological dynamic is a well-documented phenomenon in social science. The rejection of official medical advice is often a rational response to historical grievances or social contexts, rather than a simple act of ignorance. As demonstrated by studies on historical medical mistrust, the memory of past harms or a lack of connection with the source of information can profoundly influence health behaviors [2].

The final part of the paragraph shows Dr. Carlo Ruggiero's humility and scientific curiosity. While he dismisses the "theory of humors," he doesn't entirely rule out the possibility that there might be a grain of truth in the folk belief that skin eruptions can be a way for the body to rid itself of toxins. This highlights the thought process of a diligent physician working with limited knowledge, open to various possibilities even if they originate from unscientific beliefs. This approach, of being open to unexpected observations, is a testament to the scientific method and remains a valuable lesson for modern physicians and scientists facing new and unknown diseases. Even with the immense progress of modern science, this same humility remains essential; as with the initial debate over the origin of COVID-19, theories once dismissed as conspiratorial, such as the non-natural origin of the virus, have since gained a degree of plausibility and merit further scientific investigation [3]. Therefore, both in the time of Dr. Ruggiero and in the modern era, it is a crucial lesson to not a priori dismiss theories that may initially seem absurd.

1.2 From Symptoms to Science: The Diagnostic Dilemma

1.2.1 Original

As for the polymorphism presented by the infection in the first cases, I can certainly confess that I made no report [at the beginning of the epidemic], because I always believed that it was a case of simple epidemic rubella, or that morbid form that Filatow calls measles roseola and on whose etiology he does not pronounce, or even one of those forms of measles so mild and so lacking in characteristic signs as to rightly generate in many authors the clinical concept of identity between measles and roseola; and other physicians in our municipality have, in this way, interpreted these first pathological cases just like me. Because if it is true that many authors, including Barthez, Hein, Reit, Rilliet, Simon, etc., deny rubella any pathological unity in itself, considering it at most a symptom of other diseases, e.g., of some endogenous or exogenous

intoxications, it is also true that other observers, including Balfour, Broka, Burus, Stark, Ziegler and, among our own, de Giovanni, Queirolo, De Renzi, have brought such a wealth of observations and criticism as to make it considered a true autonomous morbid entity.

Murray then focused his attention on a characteristic swelling of the latero-cervical ganglia, a swelling sometimes spontaneously painful and almost always on pressure, which would be a truly pathognomonic symptom of rubella. Queirolo and de Giovanni found Murray's symptom in 70% of cases and consider it a differential characteristic between rubella and measles. However, in addition to this characteristic, Emminghaus and Hardvvay pointed out that while in measles there is a true acme in the efflorescence, in rubella there is never an acme, because a maximum of efflorescence in some areas of the body corresponds simultaneously to a state of defervescence and slight flaking in others, since one cannot speak of true desquamation in this pathological form. The intensity of the fever can, in some cases, be a good diagnostic aid, as can the Koplik spots, which we will discuss more extensively. In any case, these rules, which hold up quite well in theory, in practice present so many exceptions and so many weak points that they rightly generate difficulties such as to justify the confusion that the ancients and the moderns have made and continue to make about the two exanthematic forms.

In fact, there has been talk of benign rubellas such as that observed in London in 1671 by Sydenham and that observed in Uppsala in 1752 by Rosen, and of malignant rubellas such as that of London in 1674 and that of 1741 in Plymouth described by Huxham. Waston saw in the foundling hospital in London in 1763 and 1768 two epidemics of putrid rubella. Very severe rubella complicated with miliary fever were observed in Vira and described by Polinière and by Le Pecq de la Clôture in 1772 and 1773. The rubellas that reigned in Paris in the 6th year of the revolution were complicated with abdominal affections, in the 7th year they were sometimes associated with scarlet fever. In an epidemic of rubella observed at the end of 1800 and the beginning of 1801 by Consbruck, some children were affected by measles fever without eruption. In 1883 in Paris an epidemic of rubella was observed characterized by this fact, namely that the exanthem appeared after an invasion of whooping cough. In so many epidemics and so many series of cases, where, in fact, does true rubella end and true measles begin?

1.2.2 Commentary

This paragraph perfectly illustrates the immense challenge of clinical diagnosis in the absence of a known etiology. In 1908, physicians like Dr. Carlo Ruggiero had to rely solely on observable symptoms to differentiate between diseases. The extensive list of historical references and the detailed discussion of minute clinical signs (lymph node swelling, fever patterns, skin flaking) highlight the difficulty of this task. The final rhetorical question, "where, in fact, does true rubella end and true measles begin?" perfectly encapsulates the diagnostic uncertainty of the time.

This struggle with symptom-based diagnosis directly mirrors the initial phase of the COVID-19 pandemic. In early 2020, before widespread testing was available, doctors had to distinguish between COVID-19, the flu, the common cold, and even allergies, all of which shared overlapping symptoms like fever, cough, and fatigue. This polymorphism of presentation, as noted in the 1908 text, was a key feature in both outbreaks, complicating diagnosis and the overall public health approach. However, while measles in 1908 was a well-known, centuries-old disease causing relatively mild symptoms due to pre-existing population immunity, COVID-19 was caused by a novel virus and often presented with severe symptoms in a fully susceptible population. This is a crucial distinction. As the SARS-CoV-2 virus continues to circulate and a large portion of the global population gains immunity through vaccination or prior infection, a hypothetical new COVID-19 epidemic would likely present with milder symptoms and a clinical picture highly similar to other respiratory infections, much like the measles outbreak of 1908.

Another fascinating point of comparison is the use of historical sources. The 1908 text cites observers from as far back as 1671, illustrating a medical tradition where long-standing clinical observations were considered valid and essential to the scientific discourse. The knowledge base was cumulative and built upon centuries of shared experience. In stark contrast, modern scientific publishing places an almost exclusive emphasis on recent and even very recent publications, often rendering any work older than a few years obsolete and difficult to cite, particularly in fast-moving fields like virology. This highlights a fundamental shift in the scientific method, from a model based on accumulated historical wisdom to one driven by the most recent data.

This modern approach, however, is now subject to revision as some authors, like Nunn [4], have criticized its "extremist" nature. They argue for a reevaluation of the hierarchy of evidence in medicine, suggesting that individual observations (anecdotes) can hold a validity equal to that of randomized clinical trials. This perspective challenges the exclusive control over "truth" in medicine held by major pharmaceutical companies, which did not exist in 1908. By removing the strict hierarchy of evidence, this proposed approach could potentially undermine the dominance of corporate-funded research by giving equal weight to observations made outside of the traditional clinical trial framework.

The most significant point of departure between the two eras lies in the solution to this diagnostic dilemma. While Dr. Carlo Ruggiero and his contemporaries had to grapple with subtle clinical differences for decades, the advent of molecular biology and virology allowed for a rapid resolution in the case of COVID-19. Within months, definitive PCR and rapid antigen tests were developed and deployed, allowing clinicians to make a diagnosis based on the presence of the SARS-CoV-2 virus itself, rather than just its clinical manifestations. This ability to identify the specific pathogen, a concept unknown in 1908, fundamentally changed

the practice of medicine and public health, enabling accurate case counts, contact tracing, and the development of targeted therapies and vaccines. The journey from a clinical-based, highly uncertain diagnosis in 1908 to a lab-based, definitive diagnosis in 2020 is a powerful illustration of the progress of modern science.

1.3 Scientific Humility: Acknowledging the Limits of Knowledge

1.3.1 Original

In so many epidemics and so many series of cases, where, in fact, does true rubella end and true measles begin?

On February 2, two cases of measles were reported in the city of Spoleto, and on February 2, in the hamlet of Eggi, I reported my first case under the name of very mild measles, but throughout the month of January I had had the opportunity to observe children with exanthema playing in the middle of the streets, without fever, without Comby's ulceromembranous stomato-gingivitis, never observing Koplik's spots in cases of patients I visited on the 7th, 5th, 3rd, and 1st day preceding this "ambulatory" efflorescence; on the other hand, however, except in 3 cases, I did not have the opportunity to see the latero-cervical glandular swellings of Murray.

These cases, initially as mild as I have described them, gradually took on greater severity and by mid-February, measles in my area manifested itself clearly in a completely classic manner, and only with very rare complications; and while at first only children were affected, then adults were also afflicted.

Arab physicians Aron and Rhazes speak of true measles epidemics, and then it is necessary to jump to the 18th century, an era in which the various exanthematic forms were perfectly distin-guished, classified, and studied, emerging from the darkness in which they had lived throughout the Middle Ages. But it was only in the 19th century that we had perfect statistics of epidemics in Italy, in France, in the Faroe Islands (Panum) and in the Fiji Islands, sadly famous for the 20,000 deaths.

But what is the infectious agent of measles?

How does it propagate?

Unfortunately, our knowledge of the pathogenesis and etiology of all exanthematic diseases is still at an embryonic stage, and what we know on the matter falls within the realm of probability or requires further verification.

1.3.2 Commentary

This paragraph offers a fascinating, multi-layered insight into the dynamic nature of an epidemic and the limits of scientific knowledge. Dr. Carlo Ruggiero's personal account of the initial, confusing cases and their subsequent evolution perfectly mirrors the early stages of the COVID-19 pandemic.

First, the observation that the disease presented initially as a "very mild measles" with minimal symptoms, before progressing to a "completely classic" form affecting both children and adults, is a key parallel. This shift from a seemingly benign illness to a more severe one was also a hallmark of COVID-19's progression. At first, the virus was perceived as a distant threat causing mild respiratory illness, but as it spread and adapted to human hosts, its severe and fatal nature became tragically apparent. The virus's initial polymorphism and the subsequent broadening of its affected demographic to include adults are key epidemiological features seen in both the 1908 measles outbreak and the 2020 COVID-19 pandemic.

Second, the final section of the paragraph is perhaps the most profound. Dr. Carlo Ruggiero's candid admission that the "pathogenesis and etiology" are in an "embryonic stage" is a powerful statement of scientific humility. He openly acknowledges the vast knowledge gaps of his time, especially regarding the infectious agent and its mode of propagation. This resonates deeply with the early months of the COVID-19 pandemic, when the scientific community had to admit its own lack of understanding. Questions about aerosol transmission, the effectiveness of masks, the duration of immunity, and the existence of "long COVID" were all initially unknown. In both eras, the medical community faced a new foe armed with limited information, highlighting the timeless importance of an honest and open approach to scientific uncertainty.

1.4 In Search of the Invisible: Pathogens and Propagation

1.4.1.Original

Canon and Pielike found a slender bacillus in the blood, sputum, and nasal and conjunctival secretions of measles patients, which they believe to be specific, and a similar finding was made by Czajkowski. This author, by inoculating this germ into cultures, induced a peculiar form of fatal septicemia in mice.

Borini (Riforma Medica No. 25 — 1905) from the Perroncito laboratory never succeeded in finding any germ directly in the blood; but in cultures, he isolated a very slender double bacillus very similar to that of the aforementioned authors; by performing intrapleural injections in animals, they died in 5 days, and by injecting them directly into the blood, they died in 3. This microorganism, which is very difficult to cultivate, only develops in glycerinated agar and defibrinated blood, the cultures have no odor, do not coagulate milk, and do not generate either carbon dioxide or indole. The colonies, at first translucent and punctiform, subsequently merge.

Doehle and Behla also isolated a semi-motile, ciliated protozoan, embedded in blood corpuscles, but its specificity holds even less, as it was also found in smallpox and scarlet fever.

Giarrè and Carlini (Arch. F. Kinderheilk V. 46 Fasc. 3-6-1908) in 24 cases of measles were able to demonstrate a special bacillus in the blood of 21, similar to that of Pfeiffer, which is very dif-ficult to stain and preserve and grows slowly in hemoglobinized broth and agar. The finding was negative in 6 children who had already recovered from measles.

The most careful and accurate research was also carried out on the severe complications of measles, and especially in bronchopneumonia by Moritz, Deumann, Barbier, Weichselbaum, Guarnieri, Tobeitz, Manfredi, Quisseuer, Hutinel, Spillman, Simon, Jundell and others, who found streptococci, staphylococci, pneumococci, alone or in combination with each other and sometimes Friedlander's bacillus, but this finding undoubtedly represents nothing specific and only demonstrates the ease with which some microorganisms take hold on ground already prepared by other infectious agents. Cannata in the Bacteriology laboratory of the Military Hospital of Padua (Rivista Medica No. 10 — 1906) isolated 9 bacterial species in 5 cases of measles bronchopneumonia, three of which were fatal: Staphylococcus albus, Staphylococcus aureus, Micrococcus tetragonus, streptothrix, a bacillus similar to Löffler, a bacillus similar to Friedlander and a short, squat bacillus not well identified. He admits that the agent of measles bronchopneumonia is the symbiosis of the tetragonus with the Staphylococcus albus, a symbiosis by which the two microorganisms can acquire a very high degree of virulence.

All authors agree that blood, tears, and oral and nasal secretions are the means of transmitting the disease, a very frequent and easy transmission given the contact and community life in which children are found; and there are experimental data to this effect.

Home and Speranza provoked measles with the inoculation of the blood of people who had been affected, Alessandro Monro and Looke inoculated it with the lacrimal fluid and with the saliva collected from individuals affected by the disease; however, as for contagiousness from skin rash, Thomson had negative results by injecting glycerinated extracts of the epidermoid scales detached from the skin of measles patients into dogs. But besides direct contact, air has necessarily been admitted as a transport agent, and this to explain the onset of cases in zones very distant from the centers of infection. Dr. Leonardi, formerly a physician in Cascia, published and illustrated in the Gazzetta degli Ospedali e delle Cliniche No. 15, 1906, 600 cases of measles and, taking into account the infected and immune zones, came to the conclusion that the forward thrust of the epidemic he observed, originating in Posta and dying out in Cascia, was nothing more than the very evident result of air currents directed from south to north, currents that acted at a constant level superior to the towns of Palmaiola and Sant'Anatolia, which, being enclosed in small valleys, were not affected by the disease that nevertheless surrounded them. This study I have kept in mind, as it was conducted here in Umbria and consequently at altitudes not excessively different from those on which I made my observations, in terrain of almost the same nature, on populations with the same customs and habits and consequently subject to the same means of transmission and contagion.

1.4.2 Commentary

This dense and detailed paragraph is a crucial window into the scientific state of a world on the cusp of a major paradigm shift. It shows Dr. Carlo Ruggiero grappling with the two most fundamental questions of an epidemic: what is the pathogen and how does it spread?

In 1908, the field of bacteriology was mature, but virology was still in its infancy. Dr. Ruggiero's text is a perfect illustration of this intellectual blind spot. The scientific community, including luminaries he cites, was actively searching for the measles agent, but their tools and mindset were limited to bacteria and protozoa. They found various microorganisms - bacilli, cocci, even a "semimotile, ciliated protozoan" - but none of them were the true cause. They correctly identified that these were often secondary invaders responsible for complications like bronchopneumonia, but they failed to see the unseen, the virus that wouldn't be isolated for almost 50 years.

This is a profound lesson for future epidemics. The rapid identification of SARS-CoV-2 in 2020 was a triumph of modern molecular biology and genetic sequencing. We had the right tools for a virus. But what if the next pandemic is caused by a new kind of pathogen that doesn't fit our current paradigms? Dr. Carlo Ruggiero's text serves as a powerful reminder that our scientific models are fallible. The next "measles virus" may be something entirely different, demanding a willingness to admit the limits of our knowledge and to develop entirely new scientific frameworks, rather than trying to fit a new problem into an old solution.

The discussion on how measles spreads also presents a striking parallel to the COVID-19 pandemic. The text correctly identifies direct contact through bodily fluids as a primary transmission route, citing experimental evidence. However, it also introduces a highly speculative, yet prescient, idea: airborne transmission. Dr. Carlo Ruggiero notes how this "air" hypothesis was used to explain the spread of the disease over long distances, even citing a local study that links transmission to wind currents in Umbria.

This mirrors the early, contentious debate over the transmission of COVID-19. For months, the public health community focused primarily on droplet and surface transmission, a view that proved to be incomplete. It was only after a sustained push from aerosol scientists that the role of airborne transmission was widely acknowledged [5]. The debate itself, however, about whether the pathogen travels via direct contact or is carried by the air, is a recurring theme in epidemics, and Dr. Carlo Ruggiero's text proves that this is a very old and important scientific question.

1.5 A Network, Not a Wave: The Geography of an Epidemic

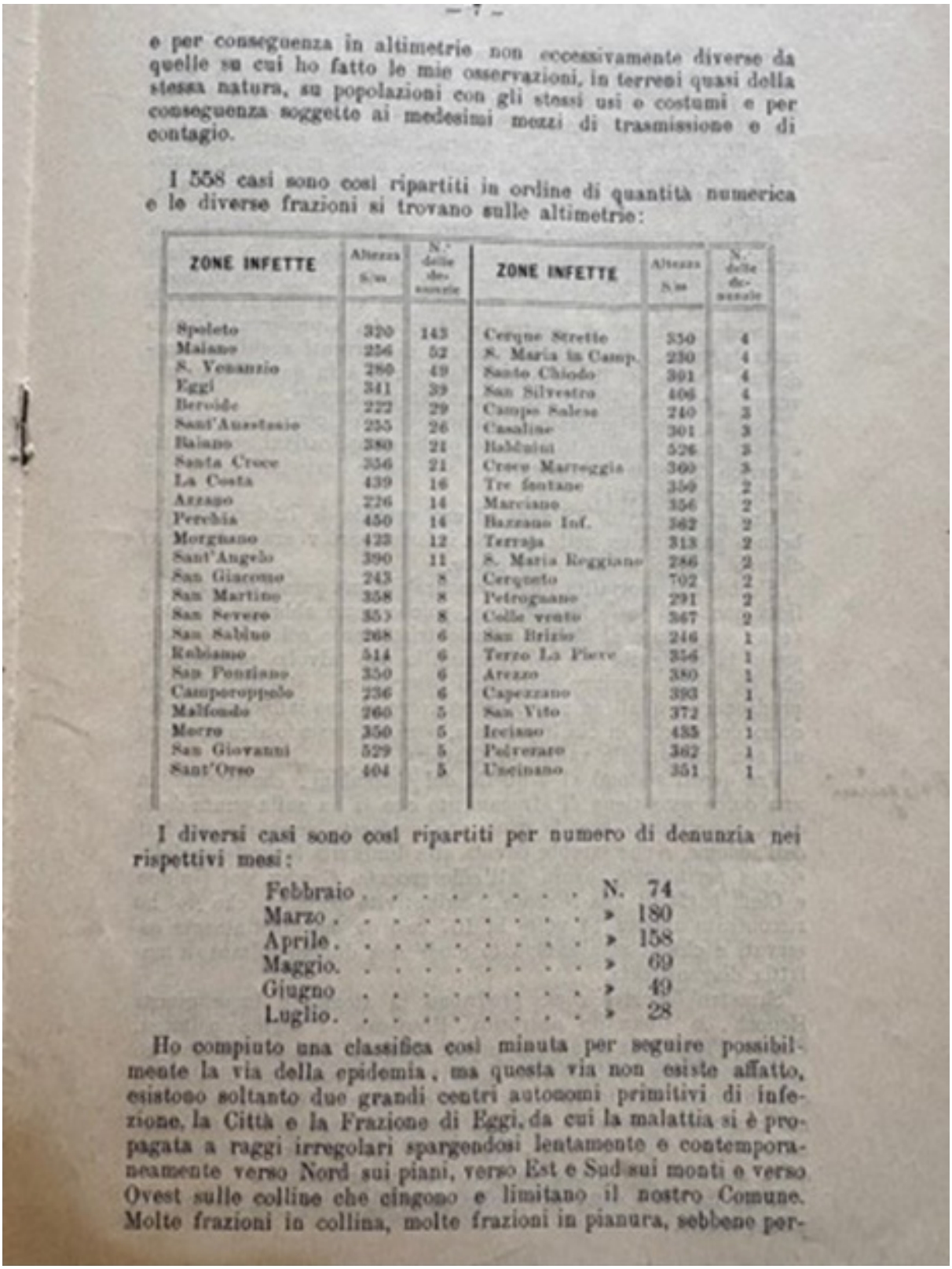
1.5.1 Original

The 558 cases are distributed as follows by monthly report:

February: 74
March: 180
April: 158
May: 69
June: 49
July: 28

I made such a minute classification to possibly follow the path of the epidemic, but this path does not exist at all; there are only two large, primitive, autonomous centers of infection, the City [Spoleto] and the hamlet of Eggi, from which the disease spread in irregular rays, spreading slowly and simultaneously northward across the plains, eastward and southward into the mountains, and westward onto the hills that surround and limit our Municipality. Many hamlets in the hills, many hamlets in the plains, although perfectly encircled by measles cases, remained, some perfectly immune, like Protte, Bazzano Superiore, etc., others almost immune, like S. Giacomo, Bazzano Inferiore, etc., and all the hamlets located towards the municipal borders in the mountains also remained perfectly immune, unlike those towards the plains which, on the contrary to the mountains, have a very active exchange and movement with the City and among themselves.

The hamlets attacked by measles, the little-attacked ones and the not-attacked ones, present the most varied altitudes, the most varied topographical positions in such a way as to absolutely ex-clude the influence of the direction of the winds which usually come from the North, while the epidemic has preferentially invaded the entire valley to the South, and also the presence of cur-rents acting at the same altitude, and the spread of the disease in this case presumably occurred through direct communication.



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e per conseguenza in altimetrie non eccessivamente diverse da quelle su cui ho fatto le mie osservazioni, in terreni quasi della stessa natura, su popolazioni con gli stessi usi e costumi e per conseguenza soggette ai medesimi mezzi di trasmissione e di contagio.

I 558 casi sono così ripartiti in ordine di quantità numerica e le diverse frazioni si trovano sulle altimetrie:

ZONE INFETTE	Altezza S/m	N.° delle denunzie	ZONE INFETTE	Altezza S/m	N.° delle denunzie
Spoleto	320	143	Cerque Strette	350	4
Maiano	256	52	S. Maria in Camp.	230	4
S. Venanzio	280	49	Santo Chiodo	301	4
Eggi	341	39	San Silvestro	406	4
Beroide	272	29	Campo Salese	240	3
Sant'Anastasio	255	26	Casaline	301	3
Baiano	380	21	Baldaini	526	3
Santa Croce	356	21	Croce Marreggia	360	3
La Costa	439	16	Tre fontane	350	2
Azzano	226	14	Marciano	356	2
Pervbia	450	14	Bazzano Inf.	362	2
Morgnano	423	12	Terraja	313	2
Sant'Angelo	390	11	S. Maria Reggiano	286	2
San Giacomo	243	8	Cerqueto	702	2
San Martino	358	8	Petroguano	291	2
San Severo	350	8	Colle vento	347	2
San Sabino	268	6	San Brizio	246	1
Rebiano	514	6	Terzo La Pieve	356	1
San Fortiano	350	6	Arezzo	380	1
Camporoppolo	236	6	Capezzano	393	1
Malfondo	260	5	San Vito	372	1
Morro	350	5	Ieciano	435	1
San Giovanni	529	5	Pelreraro	362	1
Sant'Orso	404	5	Uscinano	351	1

I diversi casi sono così ripartiti per numero di denunzia nei rispettivi mesi:

Febbraio	N. 74
Marzo	» 180
Aprile	» 158
Maggio	» 69
Giugno	» 49
Luglio	» 28

Ho compiuto una classifica così minuta per seguire possibilmente la via della epidemia, ma questa via non esiste affatto, esistono soltanto due grandi centri autonomi primitivi di infezione, la Città e la Frazione di Eggi, da cui la malattia si è propagata a raggi irregolari spargendosi lentamente e contemporaneamente verso Nord sui piani, verso Est e Sud sui monti e verso Ovest sulle colline che cingono e limitano il nostro Comune. Molte frazioni in collina, molte frazioni in pianura, sebbene per-

Figure 5: Original Table in which Dr. Carlo Ruggiero Indicates the Number of Measles Cases he Observed (in Italian, "Denunzie") in each Hamlet (in Italian, "Zone Infette"), Along with the Altitude Above Sea Level for each Hamlet (in Italian, "Altezza S/m"). From the Family Archive of Dr. Marco Ruggiero.

[Figure 5 shows the original table in which Dr. Carlo Ruggiero indicates the number of measles cases he observed (in Italian, "denunzie") in each hamlet (in Italian, "Zone Infette"), along with the altitude above sea level for each hamlet (in Italian, "Altezza S/m")].

1.5.2 Commentary

This paragraph offers a crucial insight into the unpredictable spatial dynamics of an epidemic. The detailed, on-the-ground observations of Dr. Carlo Ruggiero - who meticulously mapped the spread of the disease across his municipality - reveal that the outbreak did not follow a simple, linear path. Instead, it behaved in a complex and seemingly chaotic manner.

This observation is deeply relevant to both the COVID-19 pandemic and to future epidemics. Dr. Carlo Ruggiero's text shows that, even in a society with limited mobility compared to today, the spread of the disease was driven by human networks rather than by predictable environmental factors like wind direction. The fact that the epidemic spread from two "primary centers" and radiated outwards, while "perfectly encircled" communities remained untouched, is a powerful early illustration of a concept that became central to the COVID-19 response: the role of travel and social connections in disease transmission. The "very active exchange and movement" mentioned in the text is the 1908 equivalent of modern travel hubs and social clusters, which became the primary drivers of the pandemic's global and local spread.

The "immune" or "almost immune" communities mentioned by Dr. Carlo Ruggiero are a fasci-nating parallel to what we might call geographical or social firewalls in a modern epidemic. In the absence of a simple cause-and-effect (like wind), the data points to human behavior as the most significant variable. This reinforces a key lesson for future epidemics: effective containment strategies must focus on understanding and regulating human movement and interaction patterns, especially in the early stages when the etiology is still unknown. The meticulous, almost anthropological observation of human networks, as practiced by Dr. Carlo Ruggiero, remains a critical tool for public health officials even with all the advantages of modern technology.

1.6 From Benign to Deadly: The Hunt for an Early Warning

1.6.1 Original

In the present epidemic, the number of cases with complications has been extremely low, and the few complications, almost all affecting the respiratory system, have been very slight, except in two fatal cases! A young woman of 18 and an old woman of 72 died of bronchopneumonia; however, the second patient had serious chronic heart problems. Therefore, the mortality was almost negligible, but this fortunate event is not true of all epidemics, since, as we have seen, there have been some that have remained tragically famous, and it is precisely the malignancy with which measles can sometimes present itself that has driven and still drives many observers to establish prodromal symptoms which, if they cannot have any influence on the course of the disease in those who present them, can, according to some, have a not insignificant prophylactic value.

Among these symptoms is that of Colombini, consisting of a gentle rubbing sensation on the fingertips, felt when exerting moderate pressure on the sides of the abdomen with the hands, and which is said to be due to the decreased smoothness of the peritoneal serosa invaded by the efflorescence. Comby, with Guinon and Cioffi, speaks of an ulceromembranous stomato-conjunctivitis which I found in barely 14 cases out of 107 directly observed by me and which manifested itself in an undoubtful way only after the disease had been diagnosed. Savestre de-scribes as a prodrome the impetiginous stomatitis; Henoch, necrotic stomatitis; Rousseau, ul-ceromembranous angina; Coelon, hypertrophy of some lingual papillae, lesions which I never found. Gallezowski describes as a prodrome the conjunctival catarrh which was indeed constant in all my cases, but which is certainly not an early pathognomonic symptom of measles and which, moreover, precedes the onset of the disease too little to have a true prophylactic value.

Mennier gives value to the decrease in weight that the patient undergoes before the explosion of the disease, but the very problematic meaning and the enormous practical difficulty of such a procedure are understood a priori.

Combe considers a polymorphonuclear hyperleukocytosis as a prodromal symptom; and for Fleisch and Schossberger an early sign is a qualitative modification of neutrophil leukocytes with a jagged nucleus which would only be found in measles from 63 to 85, even 5 days before the Koplik's spot symptom (Semain Med. 24, 11.1906), but such research also lacks practicality. Such research also lacks practicality.

1.6.2 Commentary

This paragraph highlights a key feature of epidemics: the variability of their impact and the desperate search for early diagnostic markers. Dr. Carlo Ruggiero's observation of the low mortality and mild complications in his specific measles outbreak - with only two deaths in vulnerable individuals - is a powerful parallel to how different strains or variants of a pathogen can present with varying levels of severity.

The two fatal cases, an elderly woman with chronic heart problems and a young woman, underscore a timeless principle of infectious disease: vulnerability is often linked to age and underlying comorbidities. This was a defining characteristic of the COVID-19 pandemic, where the elderly and those with conditions like heart disease, diabetes, or obesity faced a disproportionately higher risk of severe illness and death. While the 1908 measles outbreak was described as benign, it still had a deadly impact on these susceptible populations, just as later, more virulent measles strains

would become tragically infamous. The fact that complications were "almost all affecting the respiratory system," specifically bronchopneumonia, is another direct parallel, as acute respiratory distress was the primary cause of death in the early stages of COVID-19.

The latter half of the paragraph is a fascinating documentation of a scientific debate on the search for "prodromal symptoms." Dr. Carlo Ruggiero meticulously lists and then systematically critiques a series of proposed early indicators, from strange skin sensations to specific blood cell changes. He concludes that these are either too rare, appear too late, or are simply not practical for clinical use. This is a direct echo of the early days of COVID-19, when the global medical community was urgently seeking a definitive symptom to identify the new virus. The loss of taste and smell (anosmia/ageusia) emerged as a potential marker [6], but as Dr. Carlo Ruggiero noted of his own examples, it was neither universal nor consistently early enough to serve as a reliable tool for widespread screening. The focus on specific blood changes (polymorphonuclear hyperleukocytosis, jagged nuclei) also mirrors early attempts to use blood work to predict or di-agnose COVID-19, reinforcing the idea that while the tools change, the scientific struggle to find a definitive early marker in a novel epidemic remains a constant.

1.7 Beyond the "Gold Standard": A Critique of Diagnostic Certainty and Lockdown

1.7.1 Original

It is the Koplik's spot that at the present moment holds triumphantly a primary position and is variously valued and is the source of multiple and unfortunately not all concordant observations.

Koplik's spots are white-bluish efflorescences with a red halo and a white center due to a fatty degeneration of the epithelium, the size of a pinhead, with a diameter between 2 to 6 mm according to Schawig, which appear in the oral cavity and more precisely on the cheek mucosa, preferably near the opening of Stensen's duct, never coalescing with each other and easily detachable. Gerhrard, Flindt, Filatow, and in our country Monti, had already paid attention to these pathological formations, but had not appreciated their importance; their scientific baptism was given by the North American pediatrician Koplik who in 1896 observed, studied, and widely described them, and considered them a precocious pathognomonic symptom of measles. Concetti, Finkelstein, Gillet, and Knòspel are of this opinion. However, this absolute assertion has gradually be-come richer in exceptions which, although they do not remove the importance of the Koplik's spot, nevertheless demonstrate that this alteration of the oral epithelium does not have the specificity one would like to attribute to it. And in fact, Michelazzi is said to have found it in a case of whooping cough and in a follicular angina, while Windowitz, Guinon, Mottaboca, and Maller are said to have found it in rubella, scarlet fever, and tonsillitis.

In any case, the very high coefficient of specificity cannot be denied, and in this, almost all observations, although numerically fluctuating, agree. I say almost all, since Belfadel never found it in 150 cases, and Aronheim found it in barely 8 out of 450 cases. But Bruning (Deutsche Medicinische Wochenschrift 1905 No. 10) in 100 patients from the Leipzig pediatric clinic found the Koplik's spot in almost all of them, appearing:

in 3 children 5th-6th day before the exanthem
» 4 » 4th day
» 7 » 3rd day
» 11 » 2nd day
» 25 » 1st day
» 17 » on the same day as the exanthem

Widowitz from Escherich's clinic found the Koplik's spot in 8% of cases. Dr. Felici from the isolation ward at the Polyclinic of Rome found it in 90%, Heubner in 97% in the prodromal period and in 72% in advanced disease. Lorand in 94%, Fuisnight in 90%. Müller in 86%. Rolly and Slawik in 85%, Michelazzi on 32 cases found the Koplik's spot in only 6. Bendix in 85%.

Valagussa in 36 cases had the Koplik's spot:
in 3 children 1st day
» 19 » 2nd day
» 10 » 3rd day
» 3 » 4th day
» 1 » 5th day »
before the exanthem.

Carcaterra in 23 cases observed in the prodromal period found it in 4 (17.4%) and Rabaioli in 140 cases found it in 102 with an appearance oscillating between 3-5 days before the exanthem. Dillon (Med. Record 16-2-07) in 230 cases observed at the Newyork Foundling Hospital — found it positive in 217, doubtful in 2, negative in 11.

Out of 107 cases observed by me, I did not find the oral spots in any after the exanthem had erupted, and out of 78 of these patients who, due to special conditions = belonging to already infected families or in the vicinity of infected houses = I was able to observe on the 9th, 7th, 5th, 3rd, and 1st day before the efflorescence, I found the spots in only 19 patients.

in 2 at the 7th day before
» 5 at the 5th day
» 11 at the 3rd day
» 1 at the 1st day

And so a question spontaneously arises: Why is there a disparity of observation for the Koplik's spot that goes from 100% of positive cases to 0%, with a very rich intermediate scale of percent-ages? The search for the Koplik's spot, especially when done in daylight, presents no difficulty that could make one doubt the different

observers... so what?

So I turned to look for the relationship between Koplik's spots and the clinical severity in the course of individual measles patients and of the epidemic in general, but as much as I searched, I found nothing exhaustive in the observations, since statistics have usually limited themselves to this: measles patients N.° x percentage y, without mentioning whether it was a severe measles or not... and I am pleased to put forward this simple observation with my brief personal statistic, that is: in a very mild epidemic in terms of severity, although very widespread, in 78 carefully and repeatedly observed cases I had 19 positive Koplik's spots = if the epidemic had been more severe, would the percentage have been the same?

But does the Koplik's spot have a prophylactic value? In pediatric wards = limited to the number of beds = perhaps yes; but in practice, certainly not, both because of the very lateness of the symptom, and because of the impossibility of any rational isolation, discarding outright the idea of a pediatric lazaretto for measles patients; who sometimes number several thousands in the same city, who are largely infants, and who would need a numerically conspicuous assistance staff... and this for a morbid form whose severity is, most of the time, minimal. Furthermore, Dillon writes that in the New-York Foundling Hospital, where children exposed to contagion were subjected to frequent and repeated examinations of the mouth and isolated as soon as the oral spots were found in them, this measure was insufficient to stop the epidemic and it appeared clear that the possibility of transmission occurred a long time before the appearance of Koplik's spots.

1.7.2 Commentary

This exhaustive and meticulously detailed paragraph is a masterpiece of scientific skepticism and data-driven analysis from the early 20th century. Dr. Carlo Ruggiero dismantles the "gold standard" of his time - the Koplik's spot - by exposing its vast statistical inconsistencies and practical uselessness. This critical approach offers profound lessons for the COVID-19 pandemic and future epidemics with unknown etiologies.

Dr. Carlo Ruggiero's struggle with the Koplik's spot mirrors the initial diagnostic chaos of the COVID-19 pandemic. In both eras, a single, definitive symptom was urgently sought. While Koplik's spots were the "pathognomonic" sign of their time, their reported prevalence varied wildly from 0% to 100%, leading to a frustrating lack of consensus. This perfectly parallels the initial reliance on the PCR test for COVID-19. While PCR was considered the gold standard, its own limitations - false negatives, a long turnaround time, and a limited supply - complicated the public health response. Just as Dr. Carlo Ruggiero's careful observation of his mild measles cases yielded a very low rate of Koplik's spots, the varying presentation of COVID-19 meant that symptoms like anosmia and fever were not universally present, challenging the idea of a single, definitive diagnostic marker.

The most poignant and forward-thinking part of this paragraph is Dr. Carlo Ruggiero's critique of the symptom's "prophylactic value." He argues that even if the Koplik's spot were reliable, it appears too late to be useful for isolation. He correctly points out the impracticality of isolating thousands of children for a disease that is, in most cases, of "minimal severity." This is a striking parallel to the global debate over non-pharmaceutical interventions (NPIs) during the COVID-19 pandemic. Measures like universal masking and lockdowns were contentious because, for a large portion of the population, the disease was not severe. Dr. Carlo Ruggiero's foresight is validated by modern science: the observation that transmission occurred well before symptoms appeared -making symptom-based isolation ineffective - is a perfect analogy for the pre-symptomatic and asymptomatic spread of SARS-CoV-2. This key epidemiological feature, unknown for decades, rendered traditional public health measures reliant on symptom-based contact tracing obsolete.

However, this critical insight also brings us to a contentious point. The acknowledgement that transmission happened before symptoms was a primary justification for the unprecedented universal lockdowns seen during the COVID-19 pandemic. The rationale was that since symptomatic isolation was insufficient, it was necessary to limit the movement and social contact of entire populations to break the chain of pre-symptomatic spread.

The effectiveness of this approach remains a subject of intense debate, with critics arguing that the widespread psychological, economic, and social damages may have outweighed the benefits. The lockdowns led to a documented surge in mental health issues, including anxiety, depression, and Post-Traumatic Stress Disorder (PTSD), particularly among children and adolescents who experienced profound social isolation [7]. Economically, they caused widespread business closures, mass unemployment, and global supply chain disruptions. Furthermore, they created a "health debt" by disrupting routine medical care and cancer screenings, the full long-term consequences of which are still unknown. This raises the critical question of whether a one-size-fits-all, draconian approach is an effective and proportional response to an epidemic, even when facing a novel pathogen. The legacy of both Dr. Carlo Ruggiero's work and the COVID-19 experience suggests that future public health strategies should be more nuanced, targeted, and focused on protecting vulnerable populations without imposing an unsustainable burden on the entire society.

This section of Dr. Carlo Ruggiero’s work also teaches us a critical lesson: in a novel epidemic, a perfect, early diagnostic sign may not exist, and relying on one can be misleading. The focus should shift from a single, elegant clinical marker to a comprehensive understanding of the pathogen's overall epidemiology, especially its transmissibility before the onset of symptoms. His work serves as a timeless reminder that scientific inquiry must be grounded in real-world data and practicality, and that the greatest discoveries often arise from challenging the most accepted “truths.”

1.8 When Common Sense Is Lost: The Futility of Universal Lockdowns and the Role of AI in Restoring It

1.8.1 Original

When the schools in the Municipality of Spoleto were closed, the epidemic, as far as I can tell, followed its own course; indeed, in my area I had the opportunity to make some paradoxical observations, to which, however, I do not give any practical value, due to the lack of so many other factors, namely, that in the hamlets where the schools were closed in Eggi, and Beroide (the villages of Camporoppo and S. Maria in Campis) the number of measles cases was 39 for each, while in the hamlets where the schools were not closed, we had, for example, Azzano with 14 cases and Bazzano Inferiore with 2, figures of a notable difference considering the population of each hamlet.

In any case, I like to note that the number of the sick rose with the years up to the 5th year of life and then gradually declined. Certainly, children not going to school, staying in homes and on the streets, had more contact with all the declared and convalescing measles patients under 6 years of age who represented precisely the largest number of those affected. And then, if it is unanimously admitted by all that measles has an incubation period of 10-12 days, what importance can the Koplik's spot, which appears in advance on the 3rd-5th day, and rarely before, have for sure prophylaxis?

I think that once an epidemic is declared, that certain general state of restlessness, that certain lack of appetite, those sudden fevers without a clear cause, that indefinable malaise that the child presents, which is an early symptom common to many infections with a somewhat long in-cubation, and which I found in all the cases I observed, even before the Koplik's spot, up to 15 days before the exanthem, can well serve as a precocious pathognomonic symptom.

1.8.2 Commentary

This paragraph is extraordinary in its relevance, offering a pragmatic and profound analysis of the unintended consequences of a seemingly logical public health measure. Dr. Carlo Ruggiero's observations are a perfect analogy for the debate over lockdowns during the COVID-19 pandemic, and they offer crucial insights for managing future epidemics with unknown etiology.

The Unintended Consequences of Lockdowns: Dr. Carlo Ruggiero's observation that closing schools did not stop the epidemic, and in some areas even coincided with an increase in cases, represents a central epidemiological paradox. This phenomenon was replicated in a striking way during the COVID-19 pandemic. The closure of schools, initially considered an essential measure, often shifted contagion from a relatively controlled environment (the school) to a less controlled one (the community and homes), favoring family and intergenerational transmission. Dr. Carlo Ruggiero correctly intuits the reason: children, not being in school, were free to interact in other contexts, coming into contact with a greater number of infected or convalescing people.

This demonstrates that containment measures that do not take human behavior into account are destined to fail. Viruses move through human and social networks; if a measure blocks one path, people (and with them the virus) will find another.

The Loss of Common Sense: A Reflection: All this leads to the heart of a fundamental debate. Why did the common sense and intuition of a humble country doctor from 1908 seem to be lost by global authorities more than a century later? The answer isn't simple, but it reflects a profound change in our approach to science, politics, and society.

The loss of this "common sense" by authorities in 2020 can be attributed to several complex dy-namics that simply didn't exist in 1908.

The Excess of Data and the Lack of Intuition: Instead of a direct, pragmatic observation like Dr. Carlo Ruggiero's, decisions in 2020 were based on global mathematical models and complex data. These models, while sophisticated, tended to oversimplify the intricate web of human interactions, ignoring the fact that people adapt and change their behavior. "Science" was perceived as superior to clinical intuition, leading to a kind of intellectual blindness.

Political and Media Pressure: In 1908, a doctor from Spoleto operated in a local context, free from the pressures of a global media cycle and instantaneous public opinion. In 2020, the fear amplified by the media and social networks created immense pressure on political leaders to "do something." Inaction was perceived as a moral and political failure. Universal lockdowns were in part a response to this need to demonstrate decisive action, regardless of their long-term effectiveness.

The Extremist Precautionary Principle: Modern society operates under the precautionary principle, which holds that when faced with an unknown threat, it's better to take extreme measures to prevent the worst. In the case of COVID-19, this mindset led to an overreaction. While caution is necessary, such an extreme approach ignored the long-term collateral damages - psychological, economic, and social - that a careful observer like Dr. Carlo Ruggiero could have foreseen.

The Loss of the "Human Factor": The distance between the epidemic (a global phenomenon) and the person (an individual in a community) became enormous. Dr. Carlo Ruggiero was a part of his community; his observations were rooted in an understanding of his patients and their way of life. In contrast, lockdown decisions were made by distant experts, focused on numbers and graphs, and not on the daily well-being of people. This disconnection meant that a simple yet fundamental intuition - that closing one place does not stop human interactions, but merely displaces them - was lost.

In summary, while Dr. Carlo Ruggiero relied on the empirical wis-

dom derived from a humble and local observation, the authorities of 2020 were guided by a mix of sophisticated models, political pressure, and a precautionary approach that superseded common sense. His legacy teaches us that, when faced with an epidemic, technology and science must serve intuition, not replace it.

The Role of AI in a Future Pandemic: In 2020, artificial intelligence was not yet evolved enough to be used extensively in global public health decisions. This raises a crucial question: would a modern AI have acted like the authorities of 2020 or like Dr. Carlo Ruggiero in 1908? A modern AI would have behaved neither like the 2020 authorities nor simply like Dr. Carlo Ruggiero in 1908. Instead, it would have sought to combine the strengths of both approaches into a more nu-anced and dynamic strategy.

The Authorities' Approach vs AI: The 2020 authorities acted based on a precautionary and monolithic approach. They used mathematical models to predict case spikes and the potential collapse of healthcare systems, and they responded with universal measures (lockdowns) to "flatten the curve." This approach, while data-driven, neglected the complexity of human behavior and the non-health collateral consequences, just as observed by Dr. Carlo Ruggiero.

Dr. Carlo Ruggiero's Approach vs AI: Dr. Carlo Ruggiero's approach was based on common sense and direct observation. He noted that general measures, like school closures, did not account for the reality on the ground (children would simply gather elsewhere) and that late diagnostic symptoms were useless for prevention. His analysis was qualitative, local, and based on direct experience.

How an AI Would Have Faced the Pandemic: A modern AI would have used the computing power of the 2020 authorities to implement the wisdom of Dr. Carlo Ruggiero on a massive scale. Instead of a single universal lockdown, it would have proposed a differentiated and dynamic strategy, taking into account a much broader set of variables. The AI would have analyzed a myriad of data in real-time, not just infection rates and hospitalizations, but also human mobility, economic data (unemployment, business closures), mental health indicators, and the geographic and social conditions of each community. Recommendations would not have been one-size-fits-all. The AI could have suggested a stricter lockdown for a densely populated urban neighborhood, while recommending less severe measures for a rural, isolated community, recognizing the different impact of the virus on different realities. It would have constantly balanced the risk of infection with the social and economic costs of each measure, seeking the most effective and sustainable equilibrium.

In conclusion, a modern AI would likely have avoided the trap of "lost common sense." It would have demonstrated that the wisdom of a single country doctor can be applied on a global scale, not in a universal way, but with the customization and dynamism needed to face the complexity of human behavior and the challenges of a global pandemic.

The Search for Early, Non-Specific Symptoms: The second part of the paragraph reinforces another fundamental intuition. Failing to find a reliable and early specific symptom (like the Koplik's spot), Dr. Carlo Ruggiero relies on more general and less definitive clinical signs: restlessness, lack of appetite, and a general malaise. He claims to have observed them much earlier than the rash, up to 15 days before. This choice to favor a set of non-specific but early symptoms, rather than a specific but late sign, is a lesson for every epidemic.

During COVID-19, the medical community initially focused on specific indicators like the loss of smell and taste, which later proved not to be universal. Dr. Carlo Ruggiero's approach of observing an "indefinable malaise" as a first sign is a reminder that in a new epidemic, before the pathological mechanisms are known, the simplest and most general clinical observations can be the most valuable for the early identification of cases.

Lessons for the Future: Dr.Carlo Ruggiero's observations offer two crucial lessons for future epidemics with unknown etiology.

Targeted Strategies vs. Generic Measures: "Universal" containment measures like school closures or total lockdowns can have unexpected and counterproductive consequences. Future responses should focus on more targeted and flexible strategies that consider the complex network of human interactions and social and economic costs.

Reliability and Practicality of Symptoms: In an unknown epidemic, the search for a perfect "pathognomonic sign" may be in vain and can distract attention from less specific but earlier symptoms, which can prove more useful for case identification and contact tracing. Dr. Carlo Ruggiero's wisdom lies in his ability to adapt his diagnosis to the reality of the facts, preferring the pragmatic over the ideal.

1.9 A Scientific Legacy Vindicated: The Paradox of Cross-Protection. A Prescient Observa-tion: Heterologous Immunity, and the Future of Pandemic Preparedness

1.9.1 Original

I began the smallpox vaccinations on April 5, 1908, in the midst of a full-blown epidemic, follow-ing the usual annual municipal order, and after the procedure was completed, to my great aston-ishment I made the following observations:

out of 113 vaccinated children, 105 did not contract measles.

out of only 12 measles patients I vaccinated, the outcome was negative in all.

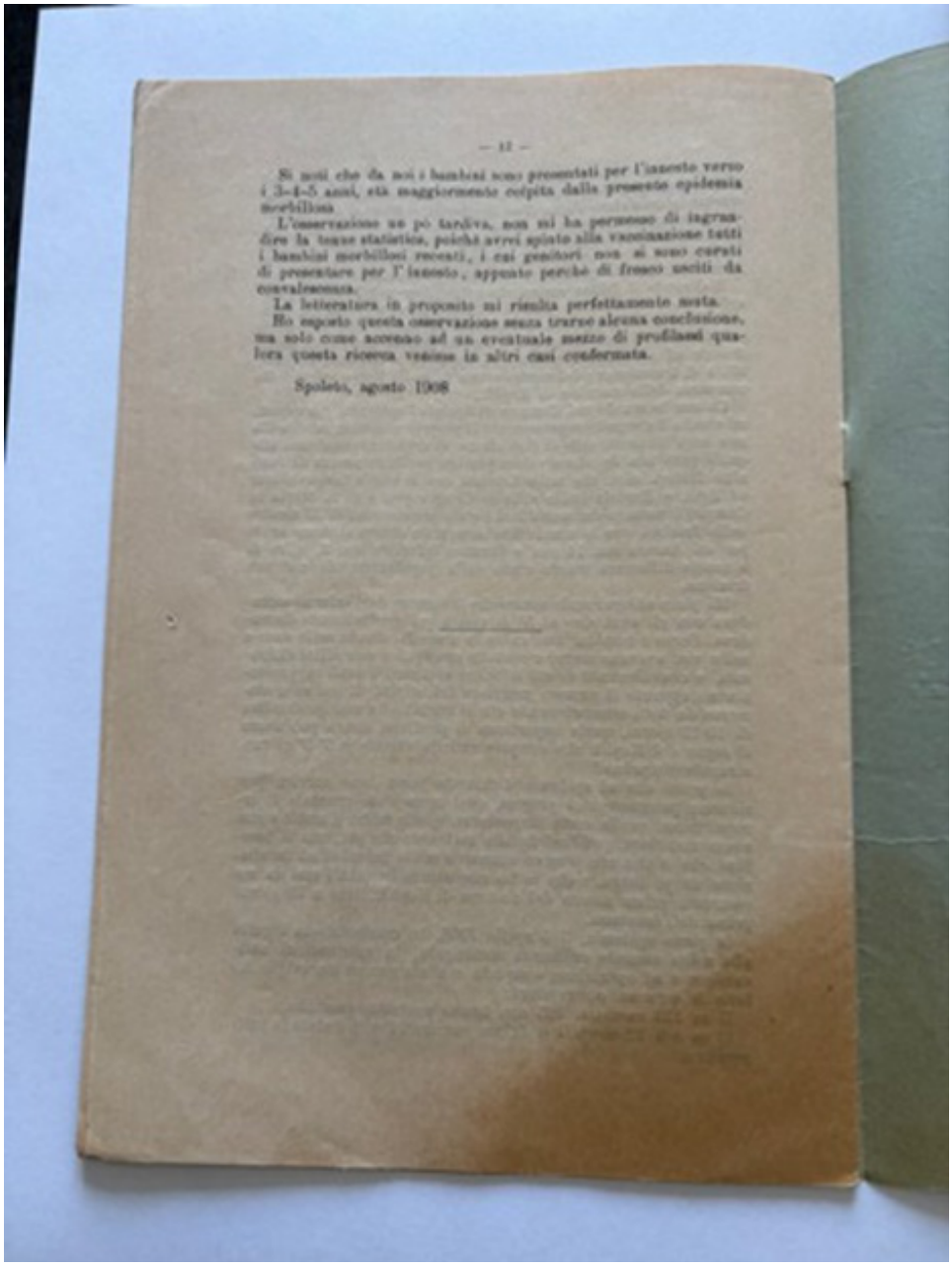
It should be noted that here, children are presented for the inoculation around 3-4-5 years of age, which is the age group most

affected by the current measles epidemic.

This somewhat late observation did not allow me to expand the small statistic, as I would have urged all recent measles-stricken children, whose parents had not bothered to present them for inoculation, precisely because they had just emerged from convalescence.

The literature on the subject seems to me to be perfectly silent.

I have presented this observation without drawing any conclusions, but only as a hint towards a possible means of prophylaxis should this finding be confirmed in other cases.



— 11 —

Si noti che da noi i bambini sono presentati per l'innesto verso i 3-4-5 anni, età maggiormente colpita dalla presente epidemia morbillosa.

L'osservazione un po tardiva, non mi ha permesso di ingrandire la tenue statistica, poichè avrei spinto alla vaccinazione tutti i bambini morbillosi recenti, i cui genitori non si sono curati di presentare per l'innesto, appunto perchè di fresco usciti da convalescenza.

La letteratura in proposito mi risulta perfettamente nulla.

Ho esposto questa osservazione senza trarne alcuna conclusione, ma solo come accenno ad un eventuale mezzo di profilassi qualora questa ricerca venisse in altri casi confermata.

Spoleto, agosto 1908

Figure 6: The Final Page of the Original Article Along with the Date and Place it Was Written: Spoleto, August 1908. From the Family Archive of Dr. Marco Ruggiero.

[Figure 6 shows the final page of the original article, containing these highly significant words, along with the date and place it was written: Spoleto, August 1908.]

1.9.2 Commentary

The seemingly simple observation made by Dr. Carlo Ruggiero in his 1908 paper - that children vaccinated against smallpox appeared to be protected from or less susceptible to measles - is, in hindsight, one of the most prescient insights of his time. Dismissed by the scientific literature of the day, his note stands as a testament to the power of meticulous observation and an intuitive understanding of a biological principle that would take over a century for mainstream science to fully appreciate. This insight, once a mere footnote in a local medical paper, now offers profound lessons for the future of infectious disease management, from the COVID-19 pandemic to unknown threats yet to come.

The following paragraphs will explore the implications of this insight, delving into the scientific mechanisms behind heterologous immunity, drawing historical parallels with the work of other pioneers, and analyzing how this lost wisdom could have changed the trajectory of past and future epidemics, including the tragic 1918 Spanish Flu.

2. The Role of Smallpox Vaccination in Preventing Measles: Mechanisms of Action

Dr. Carlo Ruggiero's data, though limited, was striking: 105 out of 113 vaccinated children did not contract measles in the midst of an epidemic. At the time, this finding was an anomaly. Today, it is recognized as a key example of a phenomenon now known as heterologous immunity, or the non-specific effects of vaccines. The mechanism behind this is not based on the production of specific antibodies against the measles virus, but on the "training" of the innate immune system.

The smallpox vaccine, which uses the live vaccinia virus, is a powerful immune stimulant. When administered, it doesn't just prompt the body to create antibodies to fight smallpox; it also induces broader changes in the immune system. This process, termed "trained innate immunity," involves epigenetic reprogramming of innate immune cells, such as monocytes and NK cells. This reprogramming makes these cells more reactive and robust, allowing them to mount a stronger, faster response to a wide array of unrelated pathogens, including the measles virus. While not offering complete protection, this heightened state of alert could be enough to either prevent in-fection or significantly mitigate its severity [8].

3. Heterologous Vaccinations and Cross-Protection

The concept of heterologous immunity extends far beyond Dr. Carlo Ruggiero's specific observation. It challenges the long-held dogma of vaccinology, which assumes a "one vaccine, one target" model. In fact, many vaccines, particularly those containing live attenuated viruses or bacteria, have demonstrated similar non-specific effects.

A prime example is the BCG vaccine (Bacillus Calmette-Guérin), originally developed for tu-berculosis. Numerous studies, most notably those conducted by scientists like Peter Aaby in Guinea-Bissau, have shown that the BCG vaccine significantly reduces all-cause mortality in children, far exceeding its protective effect against TB alone. It has been linked to a reduced in-cidence of respiratory infections, malaria, and even neonatal sepsis [9].

The primary mechanisms are believed to be the same: epigenetic changes that "train" the innate immune system and, to a lesser extent, cross-reactive T-cells that are primed to recognize shared epitopes (molecular targets) across different pathogens. For decades, these observations were dismissed as statistical noise or confounding factors, but the evidence base has grown too strong to ignore.

4. A Comparison with the Work of William Coley

Dr. Carlo Ruggiero's work finds a remarkable parallel in the efforts of his American contemporary, Dr. William Coley Around the same time, Dr. Coley, a surgeon, observed that cancer patients who developed a bacterial infection would sometimes experience spontaneous tumor regression. Following this insight, he developed "Coley's Toxins," a mixture of killed bacteria that he injected into cancer patients to stimulate a powerful immune response.

Both men were working from the same fundamental premise: that the immune system, when stimulated in an unexpected way, could have profound, systemic effects on the body's ability to fight disease. While Dr. Carlo Ruggiero was working with infectious diseases and Dr. Coley with cancer, they were both, in a sense, pioneers of immunotherapy. Their methods were based not on the targeted, reductionist approach that would come to dominate 20th-century medicine, but on an intuitive understanding of the immune system's holistic, interconnected nature. Their reliance on meticulous observation and their willingness to explore "paradoxical" findings made them intellectual siblings, decades ahead of their time [10].

5. Why Dr. Carlo Ruggiero Found Nothing in the Literature

It is no surprise that Dr. Carlo Ruggiero found "the literature... perfectly silent" on his observation. In the early 20th century, the medical world was entirely captivated by the triumph of germ theory. The focus was on identifying a single pathogen for a single disease and developing a specific, targeted intervention. The idea of a vaccine for one disease providing protection against an unrelated one ran counter to this prevailing scientific paradigm.

Furthermore, medical research was highly formalized and driven by laboratory science. A solitary doctor's anecdotal observations, no matter how keen, were unlikely to be published or taken seriously without a clear, demonstrable mechanism of action, something that was impossible to prove with the technology of the era. Dr. Carlo Ruggiero's data was dismissed not because it was false, but because it was an inconvenient truth that did not fit the

established scientific narrative [11].

6. The Impact of a Heeded Observation on Epidemic Management

Had Dr. Carlo Ruggiero's observation been taken seriously and explored, it could have funda-mentally altered the trajectory of medicine. It might have led to the early discovery of trained innate immunity, shifting immunology from a purely reductionist focus on specific antibodies to a more holistic understanding of the immune system's broad capabilities.

In the context of epidemic management, this would have created a paradigm of prophylaxis through immune modulation. Instead of waiting for a new, specific vaccine, public health author-ities could have employed existing, broadly effective vaccines as a first-line defense to blunt the severity of a novel outbreak. This would have provided a crucial bridge of protection while spe-cific vaccines were developed, potentially saving countless lives and reducing the strain on healthcare systems.

The Hypothetical Proof of 1908's "Common Sense": This observation is extraordinary and links Dr. Carlo Ruggiero's foresight to one of the greatest health catastrophes in history. The hypothesis that his intuition, if taken into consideration, could have mitigated the Spanish Flu is fascinating and deserves a profound analysis.

The Spanish Flu, which spread starting in 1918, a decade after Dr. Carlo Ruggiero's observation, was an epidemic of unknown etiology, just like measles was in his time and COVID-19 in ours. The reasoning - that a timely smallpox vaccination could have saved millions of soldiers and ci-vilians - is based on a solid scientific logic that we now understand better as trained innate im-munity.

The Role of Timing: Most soldiers had already been vaccinated against smallpox as children, but the stimulation of the innate immune system is most effective when it is recent. A new injection of the smallpox vaccine, administered at the beginning of the Spanish Flu epidemic, could have "awakened" the immune system. This would have made their non-specific defenses more ready to fight the new influenza virus, reducing the severity of symptoms, the viral load, and, consequently, mortality.

Reduction in Mortality: The Spanish Flu was particularly lethal due to a "cytokine storm" that triggered a hyper-inflammatory immune response, especially in young adults. Trained innate immunity, while not blocking the virus, could have modulated this overactive immune response, making it more controlled and less deadly. Thus, even if the vaccine would not have stopped the virus's spread, it could have transformed a fatal disease into a more manageable one, saving countless lives.

However, it is crucial to consider that the context was extremely chaotic. The speed of the virus's spread during wartime, the unsanitary conditions in the camps, and the lack of a global strategy would have made large-scale implementation extremely difficult.

The Legacy of Dr. Carlo Ruggiero: The question is not just about a historical gap, but highlights a missed opportunity. Dr. Carlo Ruggiero's observation could have provided an instrument for immediate prophylaxis in an era where no effective therapy against the flu existed. If the scientific community had taken his empirical "common sense" seriously, a strategy could have been developed to test the efficacy of existing vaccines against emerging pathogens.

This hypothetical application would not only have saved lives, but it also would have advanced the current understanding of heterologous immunity by decades. The intuitions of Dr. Carlo Ruggiero and Dr. William Coley teach us that the immune system is a holistic mechanism and not a collection of isolated responses. In the end, although we cannot know with certainty whether millions of deaths would have been avoided, it is scientifically plausible that Dr. Carlo Ruggiero's observation could have had a significant and positive impact, offering an extra weapon in a moment of global desperation [12].

7. Why a Similar Strategy Was Not Adopted in 2020: The medical community in 2020 was well aware of heterologous immunity, but the debate on its application was contentious. A similar strategy was not broadly adopted for several key reasons:

Lack of Definitive Evidence: While studies on BCG and other vaccines showed promising signals, the evidence was not robust enough to justify a global recommendation for off-label use. The data was from observational studies, and critics argued that the perceived effects could be due to confounding variables.

Focus on Specificity: The dominant scientific and public health mindset remained fixated on a specific, targeted solution. The focus was on developing a vaccine against SARS-CoV-2 as quickly as possible, and the mRNA and viral vector platforms were seen as the ultimate, definitive answer. Using existing, imperfect solutions was viewed as a distraction from this primary goal.

Ethical and Logistical Concerns: A global recommendation for off-label vaccine use would have raised significant ethical and logistical hurdles. It could have caused shortages of essential vaccines and created a legal and ethical quagmire. Ultimately, the risk-benefit analysis favored waiting for a proven, specific vaccine [13].

8. Implications for Future Epidemics with Unknown Etiology: The COVID-19 pandemic has reignited interest in heterologous immunity and vindicated the foresight of thinkers like Dr. Carlo Ruggiero. In the future, facing a new pathogen with unknown etiology (like HIV, for which no specific vaccine exists despite decades of research), the approach will likely be different.

First-Line Defense: For an unknown pathogen, the initial response

could involve the immediate deployment of large-scale clinical trials to test the non-specific effects of existing, safe vaccines (e.g., MMR, BCG) on the new threat. This could provide a degree of protection and blunt the impact while a specific vaccine is in development.

Broader Research Focus: The scientific community may shift its focus from a purely reductionist approach to a more holistic one, aiming to develop new "immune-modulating" therapies or even broad-spectrum vaccines that provide general protection against a range of potential viral families. This is an exciting and promising area of research.

In this sense, the legacy of Dr. Carlo Ruggiero, Dr. William Coley, and other early pioneers has come full circle. Their initial intuitions, once considered fringe, are now at the very heart of the next generation of medical research, holding the promise of a world better prepared to face the inevitable challenges of future pandemics.

9. Conclusions

The story of Dr. Carlo Ruggiero's 1908 observations reminds us that the most powerful insights in public health crises often arise not from sophisticated laboratories but from the quiet, attentive work of clinicians on the front lines. His modest record - 113 children vaccinated against smallpox, 105 of whom escaped measles during a raging epidemic - hinted at a phenomenon that modern immunology now calls heterologous immunity: the capacity of certain vaccines to "train" the innate immune system and confer broad, nonspecific protection against unrelated pathogens. At the time, this suggestion was dismissed as anecdotal noise, yet it anticipated a whole field of research that today informs discussions about BCG and MMR vaccines as interim shields during emerging pandemics.

Two crucial lessons emerge that should shape today's health policies. First, common sense grounded in local observation must be integrated with data-driven modeling. Dr. Ruggiero had the foresight to warn that blanket measures, such as school closures, simply displaced transmission rather than halting it. Contemporary pandemic plans that rely exclusively on uniform lockdowns risk repeating this error, overlooking the adaptive behavior of communities and the unintended socioeconomic fallout that can amplify health harms. A tiered response that tailors interventions to the density, mobility patterns, and vulnerability of each region can preserve essential societal functions while still curbing spread.

Second, the immune system's inherent versatility offers a rapid, low-cost first line of defense while pathogen-specific vaccines are developed. If the smallpox vaccine had been recognized as a provisional protective tool in 1918, the Spanish Flu death toll might have been markedly lower. Today, the same principle underlies ongoing trials of BCG and MMR as stop-gap measures against COVID-19 and future unknown agents. Health agencies should maintain protocols for the rapid and ethically sound evaluation of existing vaccines' off-label benefits, ensuring that supply chains, regulatory pathways, and public communication are ready to deploy them when a new threat emerges.

Embracing these insights doesn't mean abandoning rigorous scientific standards; rather, it calls for a balanced epistemology that values both high-quality experimental evidence and the experiential knowledge of clinicians who witness disease dynamics in real time. Institutional mechanisms, such as multidisciplinary advisory panels that include frontline physicians, behavioral scientists, and data analysts, can institutionalize this balance, preventing the marginalization of "intuition" that has historically delayed effective action.

Dr. Carlo Ruggiero's work also offers a crucial lesson on the future of public health. Artificial intelligence should not act like 2020 authorities with a "monolithic" approach, nor should it be limited to a 1908 doctor's local observation. Instead, the true value of AI lies in its ability to syn-thesize the two. An advanced AI system could analyze a myriad of variables in real-time - infection rates, mobility data, economic statistics, and mental health indicators - to propose differentiated and dynamic responses. It could recommend stricter measures for a densely populated urban community while suggesting lighter approaches for a rural, isolated region, constantly balancing health risks with the social and economic costs of each intervention.

In summary, the convergence of common-sense observation, heterologous immunity, and dynamic, context-aware policy offers a compelling blueprint for health authorities. By learning from the past, leveraging the innate flexibility of the immune system, and designing responsive, evidence-balanced interventions, we can transform the recurring tragedy of "unknown" pandemics into an opportunity for smarter, more compassionate, and scientifically sound public-health stewardship.

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Consent to participate

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