|  |  |
| --- | --- |
| **Chapter 24:** |  |
| **Challenges in Devising a Diagnostic Approach for Idiopathic Conditions Surging to Pandemic Situations** | |
|  |  |
| Debayan Baidya |  |
| Department of Medical Laboratory Technology |  |
| Bapubhai Desaibhai Patel Institute of Paramedical Sciences, Charotar University of Science & Technology, Changa |  |
| Anand-Gujarat, India- 388421 |  |
| [debayanbaidya.bt@charusat.ac.in](mailto:debayanbaidya.bt@charusat.ac.in) |  |
|  |  |
| Khushal Patel |  |
| Department of Medical Laboratory Technology |  |
| Bapubhai Desaibhai Patel Institute of Paramedical Sciences, Charotar University of Science & Technology, Changa |  |
| Anand-Gujarat, India- 388421 |  |
| [khushalpatel.bdips@charusat.ac.in](mailto:khushalpatel.bdips@charusat.ac.in) |  |
|  |  |
| Hemant Kumar |  |
| Department of Medical Laboratory Technology |  |
| Bapubhai Desaibhai Patel Institute of Paramedical Sciences, Charotar University of Science & Technology, Changa |  |
| Anand-Gujarat, India- 388421 |  |
| [hemantkumar.cips@charusat.ac.in](mailto:hemantkumar.cips@charusat.ac.in) |  |
|  |  |
| Ketankumar Panchal |  |
| Department of Biological Sciences |  |
| P. D. Patel Institute of Paramedical Sciences, Charotar University of Science & Technology, Changa |  |
| Anand-Gujarat, India- 388421 |  |
| [ketanpanchal.as@charusat.ac.in](mailto:ketanpanchal.as@charusat.ac.in) |  |
|  |  |

**ABSTRACT**

The rapid surge of idiopathic conditions into pandemic-scale outbreaks presents a significant challenge for global health systems. Traditional empirical diagnosis fails when symptoms arise without a clear correlation to known pathogens, leaving clinicians and researchers in a state of uncertainty. The absence of an identifiable etiology—whether microbial, environmental, or a complex interplay of factors—creates diagnostic roadblocks, leading to delayed responses and increased morbidity. Environmental variables, seasonal fluctuations, and potential cross-kingdom zoonotic events further complicate pathogen identification and transmission dynamics. A key limitation in these situations is the lack of baseline data, hindering comparative analysis and predictive modelling. Understanding the general architecture of pathophysiology during such outbreaks is crucial to developing effective diagnostic strategies. However, devising identification methods and rapid tests in real-time remains challenging due to evolving case definitions and limited validation frameworks. Furthermore, ensuring the scalability and interoperability of diagnostic tools across diverse healthcare systems adds another layer of complexity. This chapter explores these challenges and highlights the need for adaptive diagnostic frameworks that integrate multi-omic approaches, real-time surveillance, and global data sharing. Addressing these gaps is critical to mitigating future outbreaks of unknown origin and enhancing preparedness for emerging global health threats.

**Keywords:** Idiopathic Symptoms, Pandemic, Cross-Kingdom Zoonosis, Diagnostics Tests, Scalability.

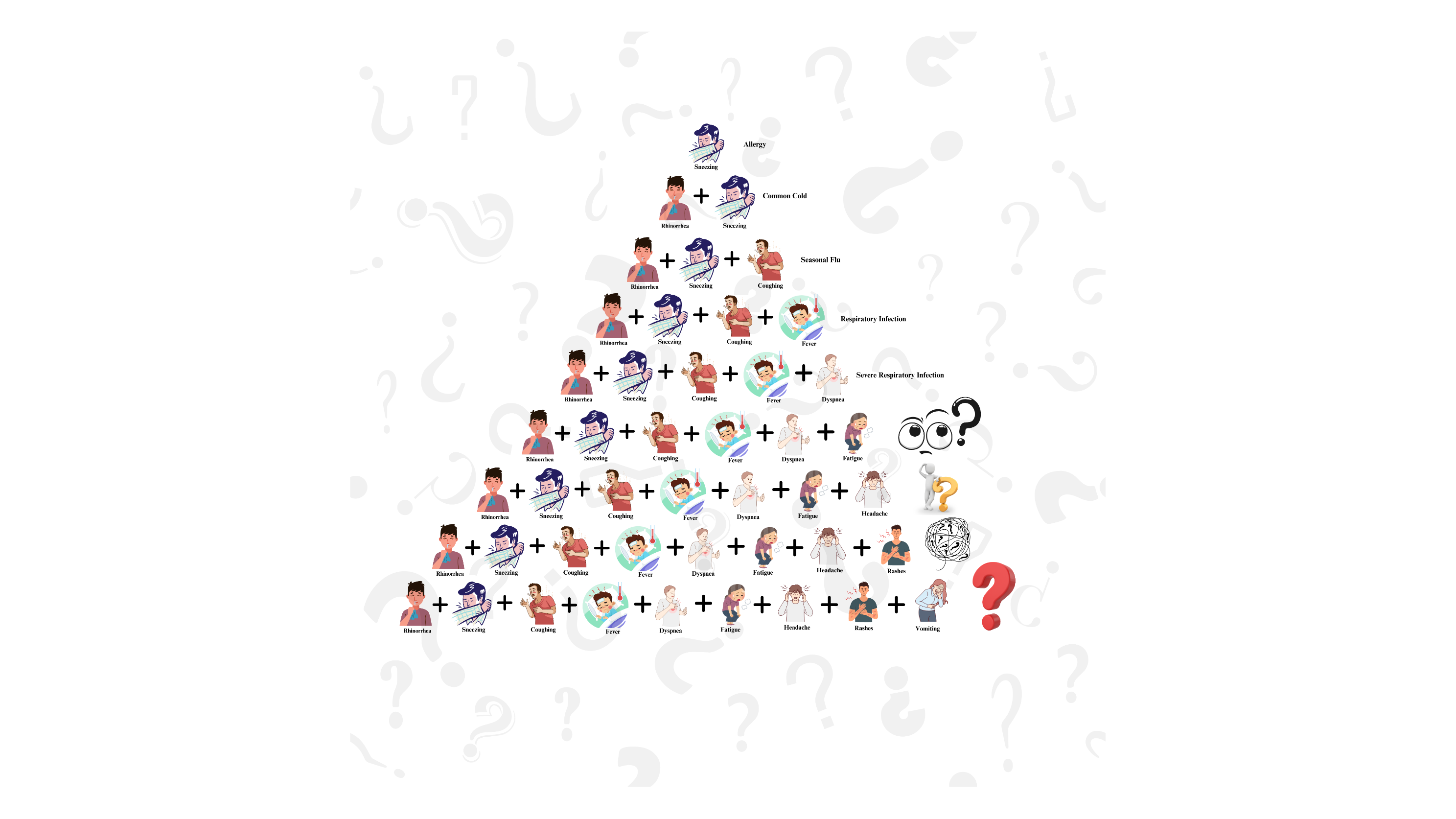
1. **INTRODUCTION**

Diagnostic tests and approaches are the shields of medical sciences, which help medical professionals to diagnose and mitigate the onset conditions of patients' pathology. The understanding of diagnosis always comes through the correlation of symptoms versus systemic physiology, source, and cause of pathology [1], [2]. However, devising a diagnostic procedure requires a multifaceted approach to balance finding reasons with accuracy, reliability, and reproducibility. The entire diagnostic method design is a step-by-step procedure that has to be meticulously reviewed statistically before generalized implementation [3], [4], [5]. However, if it is a systemic pathology or infection due to known and reported pathogens, in a situation where the patient's condition doesn’t exacerbate or deteriorate, traditionally, the diagnostic methods would have a conventional timeline based on the patient care approach and abiding by the guidelines[4]. What if the situations are at odds? What if there is a compendium of diversified symptoms with no correlation? What if the sources are *unknown*? What if the *unknown* hits the population? These are some of the obvious questions that arise when looking at that *unknown* and trying to devise a diagnostic method to detect that *unknown.*

Six years down the line, if we revisited when humankind observed the pandemic situation, severe acquired respiratory syndrome coronavirus 2 (SARS-COV2) and its versatile nature, which appeared as a genetic drift, wiped out millions and caused mortality since 2019 till date. The aftermath as well, corroboration quoted epidemic amidst the pandemic- mucormycosis, a fungal infection outbreak during SARS-COV2, with other incidences of coinfections such as Florona, Delmicron and the condition of long covid till date [6]. Mentioning SARS-COV2, SARS-COV1 appeared as an endemic outbreak in 2002 [7], a mini pandemic situation that took about 774 lives out of 8096 cases before it was contained [7], [8], [9]. Nevertheless, Middle East Respiratory Syndrome (MERS), marked on the calendar in early April of 2012, claimed 34.3% of mortality [10]If we look at the evidence in reports chronologically, the SARS-COV1 outbreak occurred in 2002. MERS-COV, a variant of the coronavirus outbreak, was observed in 2012, followed by SARS-COV2 incidents in 2019. In contrast, in their classical paper, Tyrrell and Bynoe reported the first-ever incidence of human coronavirus infection in 1965. [11], [12] With evidence from 1965 to 2019, the progression of the First coronavirus to SARS-COV1 to MERS-COV to SARS-COV2 is a record that raises several questions. Does it draw a pattern of vulnerability? That has to be taken seriously.

Between 1965 and the present, humankind has experienced many other pandemics, such as acquired immunodeficiency syndrome (AIDS), swine flu (H1N1), EBOLA outbreak, Zika Virus outbreak, Dengue Fever, cholera, avian influenza (H5N1), and measles, which have marked the outbreaks and caused mortality. [13], [14], [15]. With time, the clock will always be ticking towards the threat of more stable, virulent, vulnerable outbreaks of previously encountered pathogens with a new mutation. And will question our ability to understand, detect, and diagnose the onset of conditions. This chapter explains the challenges that medical professionals and scientists face to add an understanding of fight-to-flight situations for a quick diagnostic method to generalize disease detection and measures to protect, detect, and diagnose during adversities of sudden outbreaks, not only in case of the reappearance of vulnerable variant strains of old pathogens but also entirely new infections.

1. **INTRODUCING THE SUDDEN SURGE IN IDIOPATHIC SYMPTOMS AND CORRELATIONAL FAILURE FOR EMPIRICAL DIAGNOSIS.**

****

**Figure 1:** *Schematic representation of the array of symptoms and correlational dilemma*

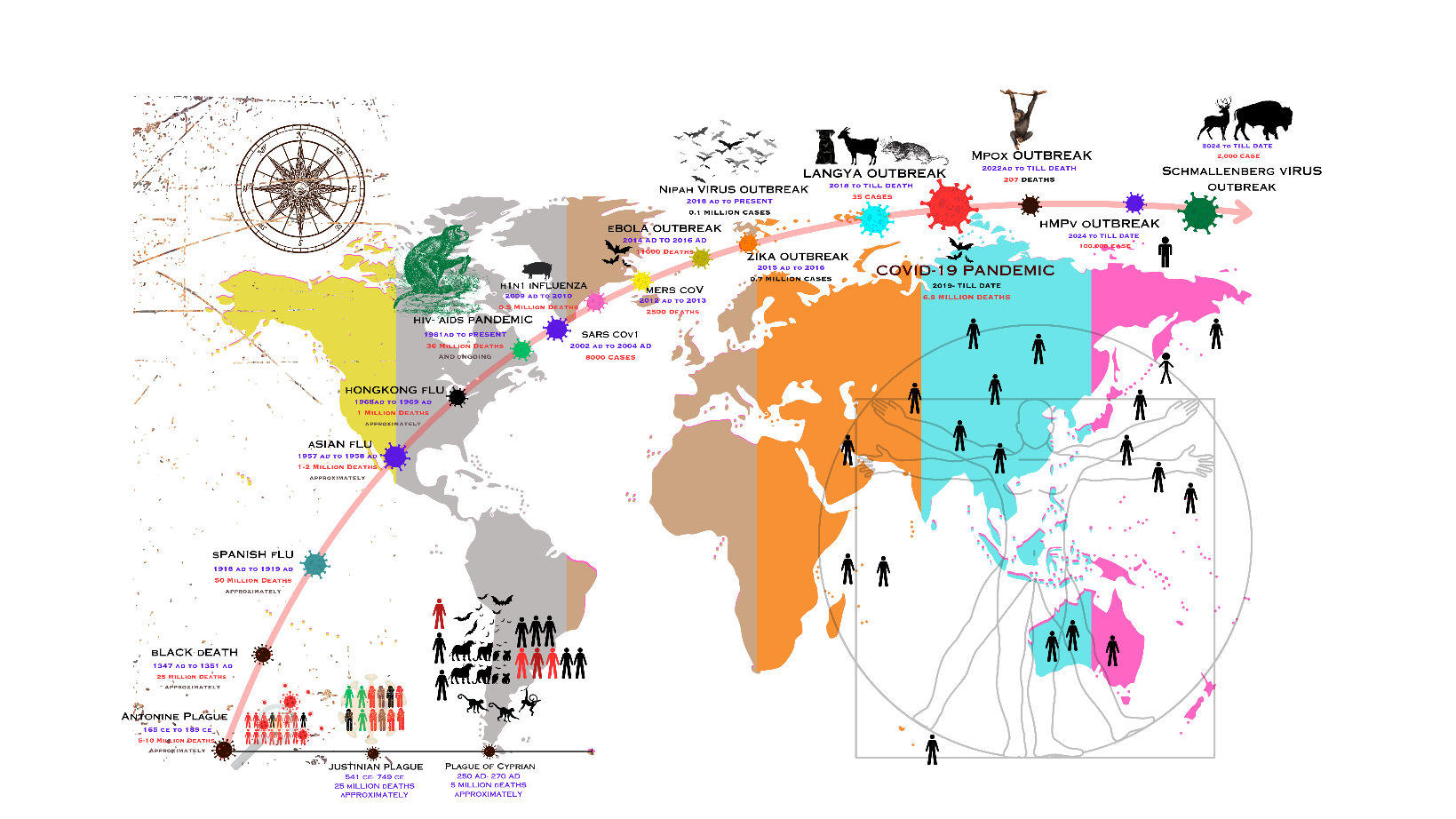
Pathology of any system has typical patterns of inflammatory responses. Correlations with the etiology create a clear understanding and indication of how to detect and mitigate the onset compendium of the symptoms. However, considering different onsets: *Onset1*: hyperthermia, exanthema- red spots on the buccal cavity, ulcerated and dry vesiculopustular crusty morphology throughout the body but with severe dyspnea and exacerbated coughing [16]; *Onset 2*: Acute respiratory distress, headache, hyperthermia, hemoptysis, arthralgia or myalgia, pain in the lower abdomen, chest pain, sore throat and fatigue [17]; *Onset 3*: Weakness, fatigue, diarrhoea and rhinorrhea, headache, dehydration [18]; *Onset 4*: Chest tightness, tachycardia, dyspnea, hypotension, pleural effusion, pulmonary failure, acute renal failure [19]; *Onset 5*: Nausea, vomiting, fatigue, anorexia, dyspnea, hyperthermia, leucopenia, thrombocytopenia [20], and *et cetra*. Considering the onsets mentioned above, reporting at the start of a day to the emergency department of a secondary hospital one by one with mild to severe patterns, reporting in numbers, ones, tens, hundreds with limited resources on the verge of getting utilized and depleted and more such cases in-coming to the department. What can be the source? Where to look? Which system first? How do we detect it? Which parameters are to be considered? Is it novel? What pathogen can it be? Is it oriented to systemic conditions? Can it be due to comorbidity? Is it contagious? Will it lead to mass mortality?

Such technical confusions are evident for medical professionals dealing with such onsets of idiopathic symptoms, where fundamentals of pathology question the medical diagnostic compatibility of the professionals in diagnosing the conditions with empirical methods and stabilizing the patients with no clue where to look. And what to confirm? Technically, the patients' conditions remain so dichotomous that what's next? It is also questionable. However, the most standard practice for the medical professional is to stabilize the patient and treat it accordingly with the existing medical knowledge.

With clusters of symptoms mentioned in *Onset 1-5*, it is imperative to consider every symptom equally without prejudice to a particular correlation and jumping to a conclusion; however, if any of the symptoms are ignored or skipped, it may provide misdiagnosis, i.e. *Onset 1* can be viral exanthems or hand foot mouth disorder (HFMD) [21], possibilities that it can be herpes simplex virus as well [22]; Likewise, Onset 2 can be interpreted as sepsis for the other onsets mentioned. [23], pneumonia [24]; for *Onset 3* can be indicative of viral gastroenteritis and stomach flu [25]; *Onset 4* can be easily understood as pulmonary embolism and pneumonia with some comorbidities [26], [27] And *Onset 5* can be presented as a classical case of severe dengue fever. [28]. From nowhere while looking at the *Onset 1-5,* it could have been interpreted as the Antonine Plague[16] SARS-COV2[17], Ebola virus disorder [18], Hantavirus Infection [19] and Langya virus infection [20] respectively in the first place. It indicates cognitive bias, which is quite common in the prevalence of misdiagnosis. [29].

Misdiagnosis- an altogether cognitively biased decision-based phenomenon that has a devastating aftermath leading to drug-induced pathology and opens the gate of unknown aftermaths, pathological conditions, and infections, which at times is responsible for multiorgan comorbidities leading to mortality[30]. Reports have mentioned a lack of understanding of specific onset conditions, with unprecedented backfires of completely different symptoms of entirely different systems due to the repurposing of drugs to treat the symptom up hand *viz.* Certain tyrosine kinase inhibitors used for pulmonary fibrosis need specific attention to the patients and should only be prescribed to patients with healthy kidneys because, irrespective of the conditions of the lungs, the mentioned drug can reasonably lead to renal failure. [31]. Even several reports suggest that the use of ꞵ-lactam antibiotics floods the storm of peptidoglycan in the system, coins and opens the gates for unprecedented mycosis in comorbid patients.[32]. Whom to blame? Are the mentioned drugs not good? A matter of fact is the circumstances where the diagnostic correlation and the empirical methods fail to take calculative risks to treat the onset condition rather than dealing with the aftermath. The same conditions do have merit to arise when repurposed drugs are poorly understood during the sudden surge of unrelated idiopathic symptoms in outbreaks.

1. **AN OUTBREAK IN POPULATION WITH NO UNDERSTANDING OF WHAT'S NEXT?**

****

**Figure 2:** *Comprehensive timeline of several documented outbreaks in the course of human civilization*

About 8.3 billion humans residing on 7 continents and 195 countries with different demography and geography are a mark of human existence on the earth, surviving to the fittest and protecting oneself from extinction. Nevertheless, the fear and threat of the pandemic's emergence remain perplexing for the population, especially those who lack a rudimentary understanding of contagious disease and health responses. However, the source of contagion, which appears more hazardous than the actual pathogen, is misinformation[33]. More than the population knew about something that cost them their lives was misinformation, which creates a state of anarchy and chaos, with trust issues as well with the healthcare authorities due to lack of communication [33], [34]. Miscommunication not only with the medical professionals but also among regular people with the benefit of the doubt who might have contracted such symptoms and whether the medical professionals are genuinely aware of the severity of the conditions[33].

On the bigger picture, the healthcare administration counts the number of people in the population and tries to isolate and quarantine to stop the chain of spreading the disorder. Uncertainty manifests in every situation with no clue. Key challenges appear in trust, scientific understanding, social behaviour, information misinformation, mental health, restrictions, and lockdown, which are the essential domains where the threat of outbreaks questions the integrity. However, loneliness, depression, economic setbacks, fear of missing out, being caged, anxiety, anorexia, polyphagia, anger and several other mental disorders[35] Reports suggest such encounters of mental health of people quarantined during lockdown compelled people to commit suicides [36], [37].

It might not be difficult for every patient to suffer severe conditions where the body system doesn’t cooperate or has vivid symptoms depending on individual immunity. However, the threat during an outbreak is always the masses in the population, which either explicitly or psychologically deprives the population[33], [35], [36], [37]. More enormous challenges than the population and health are the capacity to control, observe properly, surveillance, treat, data collection, availability of resources, supply chain of resources, etc., directly or indirectly proportional to economics[38].

1. **LACK OF UNDERSTANDING OF THE ETIOLOGY: PATHOGEN-NO-PATHOGEN; SOURCE-NATURE-MEDIUM-ONSET- ONSET PANDEMONIUM**

Understanding the root cause of any disorder requires careful research and development, documentation and re-verification. Unlike humanity, which has observed numerous pandemics in the course of civilization in this century, the Antonine plague, which led to 10% mortality in the Roman Empire, might have been caused by smallpox or measles, remains under debate for historians and epidemiologists [16]. This was followed by the Justinian plague in the 6th century caused by *Yersinia pestis,* which, even in the 8th century, appeared as a Bubonic plague [13], [15] claimed mortality. With the understanding of the organisms in the 18th century retrospectively, meanwhile, during the era of Justinian and bubonic plague in the 6th and 14th centuries, fevers, chills, headache, muscle ache, fatigue, and weakness were determinative of the disorder in conditions of mild to severe, which led to further mortality. The organism was novel during the onset of pandemonium.

A biological agent (bacteria, viruses, fungus or parasites) potent enough to be carried by a vector that breaches the host and creates significant damage in the host body can be termed a “Pathogen”. To more clearly understand, the pathogen is derived from the Greek word “Pathos”, which indicates suffering, and “Gen” comes from the Greek word gene, which trivially refers to “producing or creating”. Pathogens leading to specific pathology have always had an alternate pathway that interferes with the body's fundamental physiology. This correlation and connecting the dots explain the pathophysiology of the onset condition and the behaviour of how the pathogen interacts with the host.

The novelty of the pathogen lies in multifactorial conditions- mentioning a few- such as its origination, adaptation, host-pathogen interactions, etc. [39], [40], [41]. If we consider an organism- the pathogen, in the course of evolution, it continuously strives to achieve stability in understanding to adaptation in adversity, a relationship where it can coexist with all superior organisms in the living system; nevertheless, the process of their striving for adaptation turns out to be vulnerable of its own in a different time. Defining a classical red queen theory collectively explains coevolution, host-pathogen interaction and the importance of sexual reproductions for the pathogens to constantly evolve, generate diversity, and remain competitive in adaptation to the host environment [42], [43].

During the Korean War of 1951, soldiers represented typical symptoms misinterpreted as regular flu and diarrhoea. Which was widespread in the population and represented symptoms such as dizziness, fever, and fatigue; they grew from mild to severe in a few weeks (2-3 weeks) with completely unrelated symptoms like inflammation and rash, redness of the eye, blurred vision and shortness of breath, leading to respiratory failure. In a similar timeline, some patients complained about respiratory distress and the mentioned symptoms affecting the pulmonary system. Another group of patients represented the excruciating abdominal pain, vomiting, dizziness and renal failure. A situation that globally reported about 150,000-200,000 cases consecutively per year, affecting the cardiovascular system, the pulmonary system and the excretory system simultaneously, created chaos in the population with a case fatality rate of about 12%- 14.3% depending upon the topography and climate during the representation of the onset dichotomously questions if it was systemic, or a pathogen associated? it was a viral infection. The conditions were later diagnosed and identified as Hantavirus infections, specifically, Hantavirus Pulmonary Syndrome (HPS) and Hemorrhagic fever with renal syndrome(HFRS). The virus was from ortho-hantavirus and the hantaviridae family. The nomenclature was derived as this infection was observed in the Korean War soldiers who were positioned and stationed at the Hantan River [19], [44], [45].

In 1954, with similar patterns of totally unrelated symptoms, a Nigerian girl represented diffused joint pain with mild jaundice, fever and headache, and a similar onset turned out to be shared in the population, which flooded with similar cases. During a thorough investigation, the clinical representation picturized the complete onset of symptoms, such as headache, fever, malaise, diffuse joint pain, rash, etc. Furthermore, if the pregnant women represented the conditions, an autoimmune Gullian Bairre Syndrome- ascending progressive weakness in lower limbs, reduction or absence of tendon reflexes, presumed cranial nerve anomaly was equivocally observed alongside microencephaly in newborns. The infection was identified as Zika Virus infection (ZIKV) with the discovery in Uganda from Zika Forest [46]. An extension of arboviruses, yellow fever virus ZIKV infects through a vector female *Aedes aeygpti* and *Aedes africanus* mosquito reported affecting about 497,593 to 14,82,701 cases in Brazil, 1,504- 31,555 cases in Columbia and about 48 countries have reported globally with confirmed ZIKV infections [46].

Almost 40 years after the previously mentioned pandemonium, Australia in 1994 reported strange influenza-like symptoms such as fever, headache, drowsiness, confusion, motor deficits, seizures, reduced consciousness, and dizziness. These symptoms progressed to pulmonary conditions such as cough, atypical pneumonia, and hypoxaemia, further leading to unprecedented severity of meningitis, myoclonus, tachycardia, and relapsing encephalitis to the extreme. The first case included common symptoms in humans and horses in Queensland, Australia; in Hendra village, four human fatalities were reported for Hendra Virus Infection (HeV). A significant outbreak with a similar set of symptoms was observed between 1989 and 1999, a decade with 105 fatalities and 265 cases in Malaysia. There were 120 cases of similar outbreaks in Bangladesh; however, in Malaysia and Bangladesh, the infections were classified as Nipah Virus Infection (NiV). The mortality rate of HeV Infections was 40%, whereas the NiV infections lie between 50% to 70%, respectively, depending upon the location of the outbreak [47], [48].

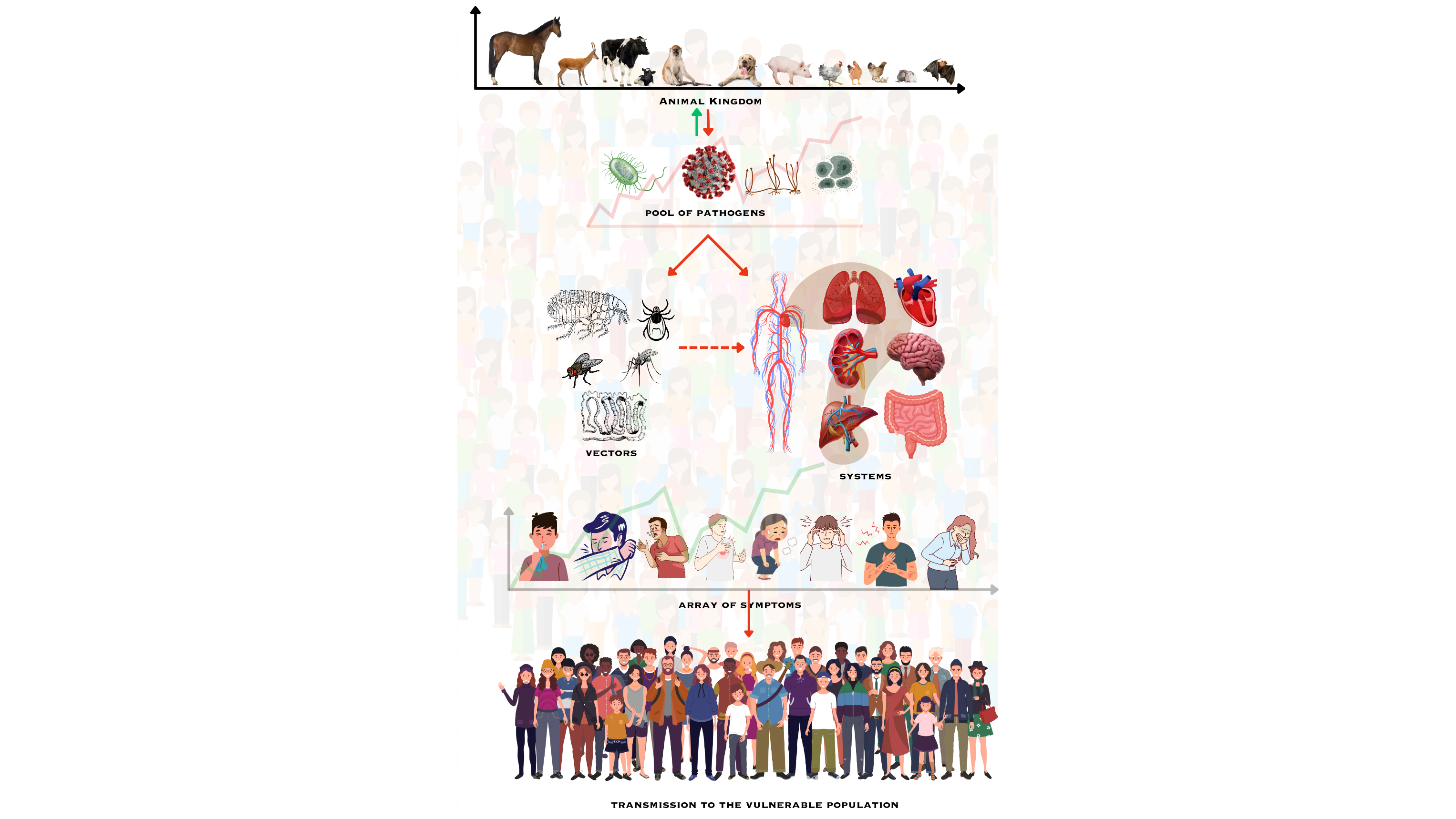
The occurrence and re-occurrence of infections always provide a platform to look into whether any outbreaks have been widespread, with a correlation of any past cases ever reported. A similar stage was obtained by the Monkeypox virus (Mpox) infection; as of 16th January 2025, a total of 1,02,997 cases are being reported globally, as mentioned by the World Health Organization (WHO) and Center for Disease Control and Prevention (CDC) in their website. Nevertheless, the first human case was documented in 1970 in the Republic of Congo amidst significant efforts to eradicate Smallpox. A ray of new infection glimpsed and vanished up till three decades ahead, with a vulnerable variant infecting about 47 cases in the United States of America in 2003, further reemerged in 2022 as a full-blown pandemic situation with symptoms in more severe forms of fever, muscles ache, lymphadenopathy and headache in prodromal till the rash formation of papules and macule on 5th day of the initial symptoms. The infection worsened the conditions as it was potent to infect the multiorgan system, leading to encephalitis, bronchopneumonia, corneal infection, secondary bacterial infection, respiratory distress and gastrointestinal infections as well [49].

Amidst the pandemic of nCovid, Shandon and Henan provinces of China between 2018-2022 reported about 35 similar cases with the clinical representation of hyperthermia, anorexia, fatigue, muscle ache, nausea, vomiting and sudden impairment of kidney and liver function with respiratory failure. The clinical assessment represented leucopenia and thrombocytopenia. The onset conditions were different from ongoing coronavirus infection; however, metagenomically, it was characterized as Langya Virus (LayV), a variant of Henipavirus isolated from the swab, which led to the isolation of the virus [20].

In the last half a decade since 2019, there has been a constant thought of terror that a new emergence or a re-emergence of infection would create anarchy in the health sector. With the proceeding and celebration of New Year's Eve, which passed as early as 3rd January 2025, an onset pandemonium among infants was reported in Bengaluru province of South India. Symptoms were cough, wheezing, shortness of breath, sore throat, fatigue, malaise, etc. The clinical representation was a combination of pulmonary and gastrointestinal systems. Upon investigation, the symptoms were associated with human metapneumovirus (hMPV), which a Dutch Virologist first reported in 2001. It had an initial outbreak in 2004, and the reemergence reported in 2025 [50].

Common symptoms, relatable pathology, the terror of the outbreak, confusion, dilemma, and failure of correlations on every onset created chaos during the outbreak. The understanding of the pathophysiology appeared to be secondary to the way of detecting the current onset, which was the top priority. Segregating the infected subject in quarantine and understanding the lifestyle pattern can help to determine the outbreak's actual cause and origin. Beyond the set mentality of the medical sciences and its guidelines, an interdisciplinary approach is required to analyse and interpret the pattern to develop a reference for detecting such sudden outbreaks. Precautionary guidelines must be established to protect against spreading epidemics in the population. The observations need to be generalized for self-care and precautions. However, fear and psychological distress during such situations appear to be the most formidable challenge. Due to such feebleness in sociopsychological political conditions and chaos everywhere, the medical and scientific fraternity lacks the time and resources to understand particular conditions completely.

1. **ENVIRONMENTAL FACTORS, SEASONAL VARIATION AND CROSS-KINGDOM ZOONOSIS**

****

**Figure 3:** *Schematic representation of Cross-Kingdom Zoonosis*

Changes in the ecosystem play a crucial role in the emergence of pandemics, as the environment's homeostasis is altered. Henceforth, opportunities for the *unknown* *pathogen to* breach the barrier to establish stability and co-survive by infecting the larger population across geographical areas. Such changes facilitate and increase the chances for pathogens from other kingdoms to transmit to humans. Migration and travel are driven by environmental factors that contribute equally to the outbreaks. People move across borders in different environments and technically unknowingly carry pathogens; such movements are often linked with demographic pressures, facilitating the urge for better living conditions. However, the new environment and new weather allow the pathogens to acclimatize and wait till favourable conditions arise to infect; such adaptations sometimes turn deleterious for the pathogens or provide a platform for them to follow the red queen theory and coexist with genetic modifications, turning vulnerable for the population [42], [43], [51].

Conditions during the Black Death, or the Bubonic Plague in the 14th Century, devastated Europe was the prime example of environmental factors influencing the pandemic; the disease was transmitted by rat fleas, which thrived in urban neighbourhoods with poor sanitization, henceforth the climate and trade routes were the environmental factors supported the widespread and was responsible for mortality[52]. Meanwhile, other examples like the resurgence of typhoid fever in warmer weather conditions [53].The H1N1 influenza virus created havoc in 2009. It is assumed that the virus originated as a crossbreed between human and animal viruses due to interactions during agricultural practices [54]. Environmental changes directed by human activities, namely deforestation, climate change, and habitat fragmentations, alter the ecosystem significantly, leading to favourable conditions for the pathogens for zoonotic spillover [55], [56]. Encroachment to wildlife increases the contact between animals and humans, introducing humans to the reservoir of pathogens susceptible to cross-kingdom spillover [57].

Significant influences have been observed in the emergence and transmission of diseases due to seasonal change, which expands the range of vectors for disease spillovers, e.g., sudden temperature surges, changes in rainfall patterns, etc., affect the distribution of several species of mosquitoes, crucial for transmission of dengue fever and malaria respectively[58], [59]. Extreme weather changes impact wildlife-human interactions and bridge gaps in inevitable outbreaks; in other words, an increase in the frequency of extreme weather changes such as floods and droughts sets the platforms for breeding grounds of vector-borne diseases to turn favourable for proliferation [60][61]. Deforestation, urbanization, and other human activities such as agriculture, livestock farming, and wildlife trades are the geosocial parameters that directly or indirectly contribute to and influence the outbreaks [61], [62].

Zoonoses, a term derived from the Greek words "zoon" (animal) and "nosos" (disease), represent a critical class of infectious diseases transmitted as a cross from vertebrate animals to humans. This transmission, often called "spillover," marks a crucial distinction from other contagious diseases primarily spread through human-to-human contact. Understanding this fundamental difference is predominant in effectively addressing these cross-kingdom infections' significant public health challenges [56]. Defining zoonosis accurately requires acknowledging the spectrum of transmission. While direct contact with infected animals is a standard route, indirect transmission pathways also play a significant role. Consumption of undercooked or contaminated animal products, exposure to infected animal excretions, and vector-borne transmission through insects such as ticks and mosquitoes represent critical avenues of transmission. The transmission mode often dictates the disease's epidemiological characteristics and shapes the strategies needed for control and prevention. Understanding these variations is essential for targeted interventions. For example, strategies to control vector-borne zoonotic diseases might focus on mosquito control programs, while foodborne zoonoses necessitate interventions focused on food safety and hygiene practices [55], [56].

The successful transfer of a pathogen from one species to another plays a crucial role in the emergence of zoonotic diseases. This process is driven by a complex interplay of biological mechanisms, not merely coincidental; they embody the intricate adaptations and evolutionary pressures that allow pathogens to navigate the inherent barriers to cross-species infection. Gaining a deeper understanding of these complexities is vital for predicting, preventing, and mitigating future zoonotic outbreaks [63]. Evolutionary pressures are crucial in determining a pathogen's ability to cross species boundaries. Pathogens that thrive in their original hosts possess traits that enhance replication, spreading, and evasion of immune responses. These advantageous traits benefit them in their primary hosts and significantly increase their potential to succeed in new hosts when they can effectively navigate the challenges of species-specific immune defense. For example, some zoonotic viruses have evolved broad host ranges, enabling them to infect various animal species. This preadaptation significantly boosts their likelihood of spilling over into human populations [64], [65], [66].

The transmission route is crucial in determining the likelihood and nature of cross-kingdom transfer. Direct contact with infected animals is a clear pathway, especially for highly infectious pathogens. The rabies virus, transmitted through an infected animal's bite, exemplifies this direct transmission. Its capacity to infect nerve cells facilitates rapid progression to the central nervous system, resulting in severe neurological symptoms and if left untreated, almost certain death. The high mortality rate associated with this virus highlights the seriousness of direct zoonotic transmission [55], [56], [67]. The consumption of infected animal products is a significant route for disease transmission. Foodborne zoonoses, which include a variety of pathogens, emphasize this pathway. Bacterial pathogens commonly transmitted through undercooked meat or contaminated dairy products include *Salmonella* spp., *Campylobacter* spp., and *E. coli* O157:H7. These pathogens often resist environmental stressors, enabling them to survive in food products under different conditions. To reduce the risk of transmission, it is crucial to practice thorough cooking and maintain strict food safety measures. Additionally, the globalization of food supply chains increases the potential spread of foodborne zoonoses over large geographical areas, posing a more significant public health challenge [68].

In recent decades, there has been a worrying increase in the frequency and severity of emerging zoonotic disease outbreaks. This rise can be linked to factors mentioned earlier, such as human-wildlife encroachment, travel and trade, climate change, and intensified agriculture[57], [67]. These changes disrupt ecological balance and increase the risk of pathogens transferring from wildlife to humans. Notable outbreaks include Ebola, Zika, and SARS-CoV-2, which highlighted vulnerabilities in global public health and underscored the urgent need for better preparedness [18], [34], [46], [69], [70].

The Ebola virus, primarily affecting West and Central Africa, highlights the severe consequences of emerging zoonotic diseases. Bats are considered the likely natural reservoir, with transmission to humans occurring through contact with infected bats or their bodily fluids. The high mortality rate and rapid spread in densely populated areas challenge healthcare systems, overwhelming their capacity and disrupting economic activity, leading to significant social and economic consequences [18], [69]. The Zika virus outbreak from 2015-2016 highlighted the dangers of emerging viruses despite a low individual mortality rate. Mainly transmitted by *Aedes* mosquitoes, Zika led to increased cases of microcephaly and neurological disorders in newborns of infected mothers, raising long-term health concerns. This situation necessitated a strong public health response focused on vector control, surveillance, and education. The outbreak also underscored global health interconnectedness, as international travel facilitated rapid virus spread. Similarly, avian influenza threats, particularly H5N1 and H7N9, involve wild birds and domestic poultry, sometimes requiring massive culling. While human infections typically arise from close contact with poultry, the risk of human-to-human transmission and new virus subtypes underscores the need for ongoing surveillance and quick responses [71], [72], [73].

The COVID-19 pandemic, driven by the SARS-CoV-2 virus, is a critical example of the significant impact of emerging zoonotic diseases. Although the precise origin of SARS-CoV-2 is still being studied, there is compelling evidence indicating a zoonotic source, most likely from bats, with the potential involvement of an intermediate host[74]. Emerging zoonotic diseases typically exhibit several common characteristics, including high transmission rates and diverse modes of transmission, such as direct contact with infected animals or individuals, vector-borne transmission, and airborne spread. Furthermore, the global distribution of these diseases is complex and influenced by various factors, including climate change, wildlife migration, human movement, and international trade. Climate change, in particular, is altering the geographic distribution of many disease vectors, thereby extending the reach of vector-borne diseases into previously unaffected areas [75].

Addressing the challenges posed by emerging zoonotic diseases demands a decisive, multi-faceted approach. Strengthening global surveillance systems is crucial for early detection of emerging threats and prompt outbreak responses. Enhancing laboratory diagnostic capabilities and epidemiological investigation skills worldwide is vital for accurate disease identification and characterization. Developing and distributing effective vaccines, therapeutics, and diagnostic tools are imperative. Public health infrastructure investment must be prioritized to ensure healthcare systems are prepared to tackle large-scale outbreaks. Long-term strategies are essential for preventing future pandemics, necessitating a comprehensive "One Health" approach that integrates human, animal, and environmental health. This holistic perspective recognizes the interconnected nature of these domains and emphasizes the critical need for collaborative efforts across disciplines to address the risks associated with zoonotic diseases [76].

1. **UNDERSTANDING THE ARCHITECTURE OF PATHOPHYSIOLOGY IN GENERAL DURING PANDEMICS**

Pathophysiology is a vital field that examines the functional changes resulting from conditions that present disorder symptoms. Focusing on the operations of organs and body systems provides valuable insights into the mechanisms of diseases, particularly concerning any underlying conditions. Understanding the signs and symptoms is essential, as they can significantly inform diagnosis and treatment strategies. This knowledge empowers healthcare professionals to develop effective interventions and improve patient outcomes [77]. The progression of disease often adheres to recognizable patterns. For instance, during respiratory infections like influenza, initial symptoms may present as flu-like conditions. However, these can rapidly escalate into more severe and critical states, such as pneumonia [24], or acute respiratory distress syndrome (ARDS). This progression highlights the importance of timely diagnosis and understanding of symptoms to prevent deterioration and manage the patient's condition effectively. Medical professionals must remain vigilant, as early intervention can make a significant difference in patient outcomes [78].

Compendium of symptoms can arise from similar infections, such as influenza, where patients may clinically present with pulmonary involvement, experiencing a range of symptoms from mild dyspnea to severe respiratory distress, including viral pneumonia and cyanosis. Even after primary recovery from influenza, some patients may face subsequent complications, as the immune system's response can create an environment where secondary bacterial and fungal infections thrive. For example, during recovery, if a patient has underlying conditions or comorbidities—such as chronic obstructive pulmonary disease (COPD), asthma, or diabetes—the risk of these secondary infections significantly increases. Patients with compromised immune systems or pre-existing pulmonary issues are particularly vulnerable and may exhibit exacerbated symptoms[79], [80], [81].

The interrelation between primary viral infections and secondary complications highlights the need for vigilant monitoring and early intervention. Early identification and treatment of these secondary infections are crucial, as they can lead to more severe outcomes, including prolonged hospitalization or even mortality. This complex interplay between various pathogens emphasizes the importance of a multifaceted diagnostic approach, recognizing that presenting symptoms may not solely stem from the primary viral infection but may also involve a cascade of challenges related to coexisting health conditions. Understanding these dynamics is essential for developing effective treatment strategies and improving patient outcomes in cases of varied and overlapping pathologies [82], [83].

Based on the recent experience with the COVID-19 pandemic, understanding the pathophysiology of the onset conditions and correlations with empirical diagnostics procedures were affected by evolving knowledge; in other words, novel infections always have limited information to be presented, and they constantly evolve with time. However, the nature of the disease tends to change as well, as we learned with the different waves of COVID-19 and vivid variants of concern (VOCs)[6]. On the other hand, cognitive impairment due to overwhelming cases, fatigue, stress and unfamiliar roles leads to the failure of empirical diagnosis due to statistical irrelevance and fallacies [84].

1. **LACK OF BASELINE DATA**

During an idiopathic outbreak and correlational failure, numbers play a vital role in understanding the onset of pandemonium. Decision-making is drastically hindered due to the lack of baseline data [85]. The absence of baseline data critically undermines the validity of a research study. Without initial measurements, it becomes nearly impossible to determine whether observed changes in health outcomes stem from the intervention itself or are influenced by other external factors. This issue is particularly significant in studies involving diseases like HIV/AIDS, where comprehensively understanding disease progression is essential for accurately evaluating treatment effectiveness.

Baseline data serve as a vital reference point for assessing changes over time and distinguishing between the disease's natural course and the intervention's effects. In HIV/AIDS research, where individual variations in disease progression are prevalent, baseline measurements can include crucial indicators such as viral loads, CD4 counts, and other relevant health metrics [86], [87]. Establishing these data points empowers researchers to confidently determine whether an intervention results in meaningful improvements in health outcomes or if observed changes reflect the disease's natural trajectory. The incorporation of baseline data is indispensable for rigorous research design, enabling valid comparisons that are essential for drawing reliable and impactful insights in medical research [51]Henceforth, the lack of baseline data creates cognitive turmoil for healthcare professionals due to an overwhelming and utterly unrelated surge of symptoms to understand, detect, and mitigate simultaneously [88].

1. **DEVELOPMENT OF IDENTIFICATION METHODS AND RAPID TESTS**

A step-by-step method is adapted to collect the baseline data through surveillance to assess the outbreak by tracking the population's response. To understand the novelty of the situations, anticipate the rapid changes and unpredicted issues while collecting the data due to no set protocol or proforma, which fundamentally challenges the situations to identify the trends for analysing the symptoms and correlate it with the demographics and segregate it from the comorbidities, if any, further to avoid the risk of bias [51], [84], [85], [88].

The critical need for rapid diagnostic tests (RTDs) defines the paradigm and its vital role in early identification, surveillance, and management, further helps in the deployment of vaccines and monoclonal antibodies[89]. Followed by a 100-day mission to identify the unknown pathogen and triple rapid framework (TRF). The TRF (Testing Response Framework) enhances the current diagnostic systems, like the World Health Organization's REASSURED criteria, by emphasizing the necessity for swift adjustments to accommodate emerging pathogens or variants. This flexibility is crucial, especially as various countries, including the U.S., have encountered difficulties implementing timely testing protocol updates. The ability to rapidly adapt testing strategies can significantly impact the effectiveness of public health responses during outbreaks, ensuring that diagnostic methods remain relevant and efficient in identifying new threats[89], [90].

Surveillance is essential for identifying pandemic threats. According to classical Robert Koch's theory, properly isolating and re-isolating the causative agents or pathogens is crucial. This isolation should be followed by whole genome sequencing to better understand public health interventions' effectiveness [89]. A unified framework for rapid diagnostic test development, evaluation, and validation during outbreaks of emerging infections is crucial. This framework is based on the feedback loop between test accuracy evaluation, modelling studies for public health decision-making, and the impact of public health interventions. This interconnected approach ensures that diagnostic tests not only meet high standards of accuracy and reliability but also align with public health goals to manage and control outbreaks effectively. It is essential to rapidly assess the performance of diagnostic tools, as timely and accurate information can influence treatment protocols, inform epidemiological models, and guide resource allocation. For instance, the rapid identification of cases can lead to quicker containment strategies, ultimately reducing transmission rates. Furthermore, the modelling studies that simulate various intervention strategies can help predict the potential outcomes of implementing a particular diagnostic test within the healthcare system. By integrating feedback from these evaluations into the development process, stakeholders can continuously refine diagnostic tests to serve public health needs better [91].

Once the test development is generalized, clinical evaluation studies become vital for generating robust data on the efficacy of detection methods for novel pathogens. These studies should be conducted through collaboration with a network of clinical partner sites, ensuring a rich tapestry of data collection across diverse demographics and varied disease presentations. By engaging multiple sites, researchers can rigorously assess the performance of diagnostic methods in real-world environments, providing invaluable insights into sensitivity, specificity, and overall effectiveness. This collaborative approach not only enhances the reliability of findings but also accelerates the dissemination of diagnostic tools—an essential element in effectively managing emerging infectious diseases. Moreover, analyzing data from a range of populations can reveal unique pathogen responses, paving the way for tailored diagnostic strategies that specifically address the needs of distinct communities. The integration of such dynamic partnerships promises to strengthen our response to infectious threats, ultimately safeguarding public health in an ever-evolving landscape [3].

The successful implementation and accessibility of rapid diagnostic tests (RDTs) require sustained financing from both the public and private sectors. Adequate funding is essential to support the research, development, production, and distribution of these tests, particularly in low-resource settings. Public financing may come from government health budgets and international aid, while private investments can be sourced from pharmaceutical companies and health tech startups. Collaboration between these sectors is vital for creating a sustainable model for RDT availability. Moreover, ongoing funding is important for quality assurance, healthcare professional training, and public awareness campaigns regarding testing significance. This comprehensive approach enhances early disease detection and treatment, leading to improved health outcomes. Additionally, it is crucial to effectively utilize diagnostic data to inform treatment and public health strategies. Stakeholders in both sectors must recognize their roles in financing and supporting the implementation of RDTs, particularly in the face of emerging health threats.

The continuous enhancement of rapid diagnostic tests (RDTs) for high-priority pathogens is essential for accurate, timely diagnoses that improve patient outcomes and public health responses. Swift pathogen identification is crucial for effective management and containment, especially during pandemics. A robust clinical validation process is necessary to rigorously assess each RDT for sensitivity, specificity, and real-world performance, ensuring accurate detection across diverse populations. Ongoing research should address limitations like false negatives and the detection of emerging strains. Collaboration among researchers, clinicians, and public health authorities is vital to establish standards for successfully implementing RDTs. Prioritizing the improvement and validation of these tests is crucial for equipping healthcare professionals to combat infectious diseases, ultimately leading to better patient outcomes and enhanced public health responses [89], [90], [91].

1. **SCALABILITY AND INTEROPERABILITY OF THE DEVISED DIAGNOSTIC TEST**

The pandemic emphatically demonstrated the critical importance of timely and accurate testing for large populations. Research institutions were ideally positioned to address the needs, particularly in smaller cities and rural areas. By utilizing their extensive resources and expertise, they can confidently establish testing centres, promote robust public health initiatives, and effectively train testing personnel, significantly improving access to testing. With strategic collaboration alongside local health authorities, these institutions can optimize testing strategies and elevate community awareness about the vital role of early diagnosis. This proactive approach not only fortifies the healthcare system’s capacity to respond to pandemics but also ensures that communities are resilient and well-prepared for future health challenges[90], [92].

Antigen Rapid Diagnostic Tests (Ag RDTs) are vital instruments in the battle against SARS-CoV-2, playing a crucial role in the early identification and swift isolation of cases during periods of heightened transmission. By delivering rapid test results, these tests empower healthcare systems to respond decisively to outbreaks. Scaling up SARS-CoV-2 testing must be intricately tied to strategic public health actions to ensure that early diagnoses not only lead to prompt isolation of positive cases but also guarantee appropriate clinical care and support. Moreover, effective contact tracing becomes an invaluable tool in breaking transmission chains, ultimately curbing the spread of the virus within our communities. When implemented thoughtfully, Ag RDTs can significantly enhance our pandemic response efforts, safeguarding public health and fostering a more resilient society [93], [94], [95].

Diagnostic tests must be agile and scalable to address supply chain shortages and urgent health crises. Their flexibility ensures effective use across various healthcare settings and adapts to evolving needs. These tests should accommodate diverse clinical specimens like blood and saliva, enhancing their utility in different patient populations. Meeting these standards is essential for tackling current public health challenges and preparing for future epidemics with confidence and efficiency [85], [89], [90], [91], [92]. Testing in centralized labs and community settings improves patient access, especially in low- and middle-income countries. This approach helps healthcare providers reach more people quickly, leading to better health outcomes and a more responsive healthcare system[96].

Interoperability, a key criterion, occurs by establishing networks of study sites with agreement and adoption of harmonized best practices and standards that can minimize variability in study design. These networks should include sites from various countries, including low- and middle-income countries, to ensure quality diagnostics are available across different settings. Enhancing collaboration among diverse research institutions can lead to better data sharing, improved methodological rigour, and more reliable outcomes. This synergy not only strengthens the overall research framework but also fosters global health equity by ensuring that effective diagnostic tools are accessible to populations in need, regardless of economic status. By prioritizing interoperability, researchers can create a foundation that supports the rapid analysis and interpretation of data, ultimately leading to quicker advancements in diagnostics for both known and emerging idiopathic conditions. Furthermore, harmonizing data collection methods and diagnostic criteria allows for a more systematic approach to identifying trends, assessing the efficacy of interventions, and guiding public health responses. With shared knowledge and resources, the scientific community can unitedly tackle the challenges posed by pandemics and other public health crises, facilitating a more agile and coordinated response to future outbreaks[97], [98].

1. **CONCLUSION**

Pandemics are inevitable in the current timelines; corroborations reported several intrinsic infections that spilt over in the timeline to cross the kingdom and infect humans need to be considered seriously by their potential of evolving into vulnerable outbreaks in future. Proactiveness would be of utmost required to battle the lacunas of the diagnostic framework to counter the nitty-gritty of the challenges, namely, accessibility, continuously evolving testing strategies, variability in the performances of the test recommended and bridging the coordination and collaboration among the healthcare system by strengthening the psychological quotient in the population.

**References**

[1] D. L. Streiner, “Diagnosing Tests: Using and Misusing Diagnostic and Screening Tests,” 2003, *Lawrence Erlbaum Associates Inc.* doi: 10.1207/S15327752JPA8103\_03.

[2] B. Lu and C. Gatsonis, “Efficiency of study designs in diagnostic randomized clinical trials,” *Stat Med*, vol. 32, no. 9, pp. 1451–1466, Apr. 2013, doi: 10.1002/sim.5655.

[3] C. Escadafal *et al.*, “Evaluating diagnostic tests during outbreaks: challenges and lessons learnt from COVID-19,” Jul. 10, 2023, *BMJ Publishing Group*. doi: 10.1136/bmjgh-2023-012506.

[4] M. Chaturvedi *et al.*, “A unified framework for diagnostic test development and evaluation during outbreaks of emerging infections,” *Communications Medicine*, vol. 4, no. 1, p. 263, Dec. 2024, doi: 10.1038/s43856-024-00691-9.

[5] C. D. Kelly-Cirino *et al.*, “Importance of diagnostics in epidemic and pandemic preparedness,” *BMJ Glob Health*, vol. 4, Feb. 2019, doi: 10.1136/bmjgh-2018-001179.

[6] S. Ojha, M. Debnath, D. Baidya, S. Shah, and K. Morje, “A Quantitative Evaluation of Knowledge, Perception, Awareness, and Preparedness of ‘Long COVID’ Among Healthcare Professionals and Students in India,” *J Radiol Nurs*, 2023, doi: 10.1016/j.jradnu.2023.10.005.

[7] J. D. Cherry and P. Krogstad, “SARS: The first pandemic of the 21st century,” Jul. 2004. doi: 10.1203/01.PDR.0000129184.87042.FC.

[8] J. D. Cherry, “The chronology of the 2002-2003 SARS mini pandemic,” *Paediatr Respir Rev*, vol. 5, no. 4, pp. 262–269, Dec. 2004, doi: 10.1016/j.prrv.2004.07.009.

[9] W. K. Lam, N. S. Zhong, and W. C. Tan, “Overview on SARS in Asia and the World,” Nov. 2003. doi: 10.1046/j.1440-1843.2003.00516.x.

[10] Z. A. Memish, S. Perlman, M. D. Van Kerkhove, and A. Zumla, “Middle East respiratory syndrome,” Mar. 28, 2020, *Lancet Publishing Group*. doi: 10.1016/S0140-6736(19)33221-0.

[11] D. Tyrrell and M. Bynoe, “Preliminary Communication CULTIVATION OF VIRUSES FROM A HIGH PROPORTION OF PATIENTS WITH COLDS,” *The Lancet*, vol. 1, pp. 76–77, Jan. 1966, doi: 10.1016/s0140-6736(66)92364-6.

[12] N. K. Jaiswal and S. K. Saxena, “Classical Coronaviruses,” in *Pathogenesis to Disease Control*, 2020, pp. 141–150. doi: 10.1007/978-981-15-4814-7\_12.

[13] J. Piret and G. Boivin, “Pandemics Throughout History,” Jan. 15, 2021, *Frontiers Media S.A.* doi: 10.3389/fmicb.2020.631736.

[14] R. C. Khanna, M. V. Cicinelli, S. S. Gilbert, S. G. Honavar, and G. V. S. Murthy, “COVID-19 pandemic: Lessons learned and future directions,” May 01, 2020, *Wolters Kluwer Medknow Publications*. doi: 10.4103/ijo.IJO\_843\_20.

[15] D. Huremović, “Brief History of Pandemics (Pandemics Throughout History),” in *Psychiatry of Pandemics: A Mental Health Response to Infection Outbreak*, Springer International Publishing, 2019, pp. 7–35. doi: 10.1007/978-3-030-15346-5\_2.

[16] Richard P. Duncun-Jones, “THE ANTONINE PLAGUE REVISITED,” in *Acta Philologica Fennica*, vol. 52, 2018, pp. 41–72. [Online]. Available: www.tiedekirja.fi.

[17] L. M. Weng, X. Su, and X. Q. Wang, “Pain symptoms in patients with coronavirus disease (COVID-19): A literature review,” 2021, *Dove Medical Press Ltd*. doi: 10.2147/JPR.S269206.

[18] T. Kratz *et al.*, “Ebola virus disease outbreak in Isiro, democratic Republic of the Congo, 2012: Signs and symptoms, management and outcomes,” *PLoS One*, vol. 10, no. 6, Jun. 2015, doi: 10.1371/journal.pone.0129333.

[19] D. C. Watson, M. Sargianou, A. Papa, P. Chra, I. Starakis, and G. Panos, “Epidemiology of Hantavirus infections in humans: A comprehensive, global overview,” Aug. 2014. doi: 10.3109/1040841X.2013.783555.

[20] S. Chakraborty *et al.*, “Langya virus, a newly identified Henipavirus in China - Zoonotic pathogen causing febrile illness in humans, and its health concerns: Current knowledge and counteracting strategies – Correspondence,” Sep. 01, 2022, *Elsevier Ltd*. doi: 10.1016/j.ijsu.2022.106882.

[21] Sarajane Ting and Rosemary Nixon, “Clinical Features Viral Exanthems,” *Clinical*, vol. 4, pp. 231–36, Apr. 2021.

[22] D. I. Bernstein *et al.*, “Epidemiology, clinical presentation and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women,” *Clinical Infectious Disease*, no. 3, pp. 344–351, Feb. 2013, doi: https://doi.org/10.1093/cid/cis891.

[23] T. B. Kortz, H. R. Sawe, B. Murray, W. Enanoria, M. A. Matthay, and T. Reynolds, “Clinical presentation and outcomes among children with sepsis presenting to a public tertiary hospital in Tanzania,” *Front Pediatr*, vol. 5, Dec. 2017, doi: 10.3389/fped.2017.00278.

[24] L. J. Quinton, A. J. Walkey, and J. P. Mizgerd, “Integrative physiology of pneumonia,” *Physiol Rev*, vol. 98, no. 3, pp. 1417–1464, May 2018, doi: 10.1152/PHYSREV.00032.2017.

[25] G. Cukort and N. R. Blacklow, “Human Viral Gastroenteritis,” 1984.

[26] M. B. Herman Chmel, *Pulmonary infections and Immunity*. Springer Science + business medianew york, 1994.

[27] V. Hespanhol and C. Bárbara, “Pneumonia mortality, comorbidities matter?,” May 01, 2020, *Elsevier Espana S.L.U*. doi: 10.1016/j.pulmoe.2019.10.003.

[28] J. G. Rigau-Pérez, “Severe dengue: the need for new case definitions,” *The Lancet*, vol. 6, pp. 297–302, May 2006, [Online]. Available: http://infection.thelancet.com

[29] L. Bray *et al.*, “Misdiagnoses in the Context of Suspected Pandemic Influenza or Coronavirus Disease 2019: A Systematic Review,” Nov. 01, 2022, *Oxford University Press*. doi: 10.1093/ofid/ofac515.

[30] E. P. Balogh, B. T. Miller, and J. R. Ball, *Improving diagnosis in health care*. National Academies Press, 2016. doi: 10.17226/21794.

[31] M. Hasegawa *et al.*, “Nintedanib-induced glomerular microangiopathy: a case report,” *CEN Case Rep*, vol. 9, no. 4, pp. 295–300, Nov. 2020, doi: 10.1007/s13730-020-00474-w.

[32] C. T. Tan, X. Xu, Y. Qiao, and Y. Wang, “A peptidoglycan storm caused by β-lactam antibiotic’s action on host microbiota drives Candida albicans infection,” *Nat Commun*, vol. 12, no. 1, Dec. 2021, doi: 10.1038/s41467-021-22845-2.

[33] G. B. Ferreira, “Conspiracy Theories in Times of the Covid-19 Pandemic: Populism, Social Media and Misinformation,” *Comunicacao e Sociedade*, vol. 40, pp. 129–148, 2021, doi: 10.17231/COMSOC.40(2021).3324.

[34] A. A. Adalja, M. Watson, E. S. Toner, A. Cicero, and T. V Inglesby, “Center for Health Security P A N D E M I C P A T H O G E N S Improving Pandemic Preparedness by Identifying the Attributes of Microorganisms Most Likely to Cause a Global Catastrophic Biological Event PROJECT TEAM P A N D E M I C P A T H O G E N S,” 2018. Accessed: Jan. 30, 2025. [Online]. Available: https://centerforhealthsecurity.org/sites/default/files/2022-12/180510-pandemic-pathogens-report.pdf

[35] M. Daly and E. Robinson, “Depression and anxiety during COVID-19,” Feb. 05, 2022, *Elsevier B.V.* doi: 10.1016/S0140-6736(22)00187-8.

[36] S. J. Zhou *et al.*, “Depression, Anxiety, and Suicidal Ideation in Chinese University Students During the COVID-19 Pandemic,” *Front Psychol*, vol. 12, Aug. 2021, doi: 10.3389/fpsyg.2021.669833.

[37] L. Sher, “The impact of the COVID-19 pandemic on suicide rates,” 2020, *Oxford University Press*. doi: 10.1093/QJMED/HCAA202.

[38] Y. Shang, H. Li, and R. Zhang, “Effects of Pandemic Outbreak on Economies: Evidence From Business History Context,” *Front Public Health*, vol. 9, Mar. 2021, doi: 10.3389/fpubh.2021.632043.

[39] M. F. Barber and J. R. Fitzgerald, “Mechanisms of host adaptation by bacterial pathogens,” Jul. 01, 2024, *Oxford University Press*. doi: 10.1093/femsre/fuae019.

[40] M. Saubin, S. Stoeckel, A. Tellier, and F. Halkett, “Neutral genetic structuring of pathogen populations during rapid adaptation,” Oct. 21, 2022. doi: 10.1101/2022.10.20.512995.

[41] M. E. J. Woolhouse, D. T. Haydon, and R. Antia, “Emerging pathogens: The epidemiology and evolution of species jumps,” 2005, *Elsevier Ltd*. doi: 10.1016/j.tree.2005.02.009.

[42] A. Papkou *et al.*, “The genomic basis of red queen dynamics during rapid reciprocal host–pathogen coevolution,” *Proc Natl Acad Sci U S A*, vol. 116, no. 3, pp. 923–928, Jan. 2019, doi: 10.1073/pnas.1810402116.

[43] A. Macpherson, S. P. Otto, and S. L. Nuismer, “Keeping pace with the red queen: Identifying the genetic basis of susceptibility to infectious disease,” *Genetics*, vol. 208, no. 2, pp. 779–789, Feb. 2018, doi: 10.1534/genetics.117.300481.

[44] Z. Bi, P. B. H. Formenty, and C. E. Roth, “Hantavirus Infection: a review and global update,” 2008. [Online]. Available: http://www.ncbi.nlm.nih.gov/ICTVdb/Ictv/

[45] T. Manigold and P. Vial, “Human hantavirus infections: Epidemiology, clinical features, pathogenesis and immunology,” Mar. 20, 2014, *SMW supporting association*. doi: 10.4414/smw.2014.13937.

[46] S. C. Weaver *et al.*, “Zika virus: History, emergence, biology, and prospects for control,” Jun. 01, 2016, *Elsevier B.V.* doi: 10.1016/j.antiviral.2016.03.010.

[47] K. T. Wong and K. C. Ong, “Pathology of Acute Henipavirus Infection in Humans and Animals,” *Patholog Res Int*, vol. 2011, pp. 1–12, Sep. 2011, doi: 10.4061/2011/567248.

[48] S. P. Luby, E. S. Gurley, and M. J. Hossain, “Transmission of human infection with nipah virus,” Dec. 2009. doi: 10.1086/647951.

[49] R. Kharwar, M. Bhatt, K. Patel, S. Patel, and N. Daxini, “A computational approach to identify natural putative inhibitors to combat monkeypox,” in *Nanotechnology and in Silico Tools: Natural Remedies and Drug Discovery*, Elsevier, 2023, pp. 285–308. doi: 10.1016/B978-0-443-15457-7.00025-3.

[50] B. L. Rao, S. S. Gandhe, S. D. Pawar, V. A. Arankalle, S. C. Shah, and A. A. Kinikar, “First detection of human metapneumovirus in children with acute respiratory infection in India: A preliminary report [1],” Dec. 2004. doi: 10.1128/JCM.42.12.5961-5962.2004.

[51] Claudia Ferreira, Marie-Françoise Doursout, and Joselito S Balingit, *2000 Years of Pandemics: Past, Present and Future*. Springer International Publishing AG, Cham, Switzerland, 2023, 2025. doi: 10.3201/eid3102.240798.

[52] John Frith, “The History of Plague – Part 1. The Three Great Pandemics,” *J Mil Veterans Health*, pp. 11–16, Apr. 2012, Accessed: Feb. 09, 2025. [Online]. Available: https://search.informit.org/doi/abs/10.3316/INFORMIT.722091776908373

[53] N. J. Saad, V. D. Lynch, M. Antillón, C. Yang, J. A. Crump, and V. E. Pitzer, “Seasonal dynamics of typhoid and paratyphoid fever,” *Sci Rep*, vol. 8, no. 1, Dec. 2018, doi: 10.1038/s41598-018-25234-w.

[54] R.V.S. Pawaiya, K. Dhama, M. Mahendran, and B.N. Tripathi, “Swine flu and the current influenza A (H1N1) pandemic in humans: A review,” *Indian J Vet Pathol*, no. 33, pp. 1–17, Jan. 2009, [Online]. Available: https://www.researchgate.net/publication/229805901

[55] M. T. Rahman *et al.*, “Zoonotic diseases: Etiology, impact, and control,” *Microorganisms*, vol. 8, no. 9, pp. 1–34, Sep. 2020, doi: 10.3390/microorganisms8091405.

[56] J. Antonio, S. Quaresma, S. Zarate, \* Correspondence, and B. B. Singh, “Zoonosis–Why we should reconsider ‘“What’s in a name?,”’” *Front Public Health*, pp. 01–05, Feb. 2023, doi: 10.3389/fpubh.2023.1133330.

[57] G. Fackelmann *et al.*, “Human encroachment into wildlife gut microbiomes,” *Commun Biol*, vol. 4, no. 1, p. 800, Jun. 2021, doi: 10.1038/s42003-021-02315-7.

[58] N. Kronfeld-Schor *et al.*, “Drivers of Infectious Disease Seasonality: Potential Implications for COVID-19,” Feb. 01, 2021, *SAGE Publications Inc.* doi: 10.1177/0748730420987322.

[59] P. Carmona and S. Gandon, “Winter is coming: Pathogen emergence in seasonal environments,” *PLoS Comput Biol*, vol. 16, no. 7, Jul. 2020, doi: 10.1371/journal.pcbi.1007954.

[60] B. Abrahms *et al.*, “Climate change as a global amplifier of human–wildlife conflict,” *Nat Clim Chang*, vol. 13, no. 3, pp. 224–234, Mar. 2023, doi: 10.1038/s41558-023-01608-5.

[61] S. Morand and C. Lajaunie, “Outbreaks of Vector-Borne and Zoonotic Diseases Are Associated With Changes in Forest Cover and Oil Palm Expansion at Global Scale,” *Front Vet Sci*, vol. 8, Mar. 2021, doi: 10.3389/fvets.2021.661063.

[62] C. J. Neiderud, “How urbanization affects the epidemiology of emerging infectious diseases,” *Afr J Disabil*, vol. 5, no. 1, 2015, doi: 10.3402/iee.v5.27060.

[63] S. Shanks, M. Ci Van Schalkwyk, and A. A. Cunningham, “A call to prioritise prevention: Action is needed to reduce the risk of zoonotic disease emergence,” *The Lancet*, Dec. 2022, doi: 10.1016/j.

[64] S. Seal, G. Dharmarajan, and I. Khan, “Evolution of pathogen tolerance and emerging infections: A missing experimental paradigm,” *Nature*, vol. 0, p. 68874, 2021, doi: 10.7554/eLife.

[65] M. Sironi, R. Cagliani, D. Forni, and M. Clerici, “Evolutionary insights into host-pathogen interactions from mammalian sequence data,” *Nat Rev Genet*, vol. 16, no. 4, pp. 224–236, Apr. 2015, doi: 10.1038/nrg3905.

[66] S. J. Schreiber, R. Ke, C. Loverdo, M. Park, P. Ahsan, and J. O. Lloyd-Smith, “Cross-scale dynamics and the evolutionary emergence of infectious diseases,” *Virus Evol*, vol. 7, no. 1, Jan. 2021, doi: 10.1093/ve/veaa105.

[67] E. H. Loh *et al.*, “Targeting Transmission Pathways for Emerging Zoonotic Disease Surveillance and Control,” *Vector-Borne and Zoonotic Diseases*, vol. 15, no. 7, pp. 432–437, Jul. 2015, doi: 10.1089/vbz.2013.1563.

[68] Leanne E. Unicomb, “Food Safety: Pathogen Transmission Routes, Hygiene Practices and Prevention,” *J Health Popul Nutr*, pp. 599–601, Oct. 2009, Accessed: Feb. 10, 2025. [Online]. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC2928085/

[69] J. J. A. van K. , C. B. E. M. R. , M. P. G. K. E. C. M. van G. \* M. Goeijenbier1, “Ebola virus disease: a review on epidemiology, symptoms, treatment and pathogenesis”.

[70] Y. C. Liu, R. L. Kuo, and S. R. Shih, “COVID-19: The first documented coronavirus pandemic in history,” Aug. 01, 2020, *Elsevier B.V.* doi: 10.1016/j.bj.2020.04.007.

[71] J. Zhou *et al.*, “Biological features of novel avian influenza A (H7N9) virus,” *Nature*, vol. 499, no. 7459, pp. 500–503, 2013, doi: 10.1038/nature12379.

[72] C. Korteweg and J. Gu, “Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans,” 2008, *American Society for Investigative Pathology Inc.* doi: 10.2353/ajpath.2008.070791.

[73] A. Goodman, “The Global Impact of the Zika Virus Pandemic: The Importance of Emergency Preparedness,” *Health N Hav*, vol. 12, no. 02, pp. 132–140, 2020, doi: 10.4236/health.2020.122012.

[74] The Lancet Microbe, “Searching for SARS-CoV-2 origins: confidence versus evidence,” Apr. 01, 2023, *Elsevier Ltd*. doi: 10.1016/S2666-5247(23)00074-5.

[75] Dr Chadia Wannous, “The Importance of the One Health Approach in Tackling Emerging and Re-emerging Zoonotic Epidemics and Pandemics,” 2024. doi: https://doi.org/10.20506/woah.3480.

[76] P. M. Saba Villarroel *et al.*, “Emerging and re-emerging zoonotic viral diseases in Southeast Asia: One Health challenge,” 2023, *Frontiers Media SA*. doi: 10.3389/fpubh.2023.1141483.

[77] G. S. Stoyanov, G. Naskovska, E. Lyutfi, R. Kirneva, and K. Bratoeva, “In Search of the Ninth Discipline: The History of Pathophysiology, with an Emphasis on Pathophysiology in Varna, Bulgaria—Celebrating 100 Years of Pathophysiology in Bulgaria,” *Cureus*, Apr. 2018, doi: 10.7759/cureus.2404.

[78] T. Siggaard *et al.*, “Disease trajectory browser for exploring temporal, population-wide disease progression patterns in 7.2 million Danish patients,” *Nat Commun*, vol. 11, no. 1, Dec. 2020, doi: 10.1038/s41467-020-18682-4.

[79] T. W. Clark, M. J. Medina, S. Batham, M. D. Curran, S. Parmar, and K. G. Nicholson, “Adults hospitalised with acute respiratory illness rarely have detectable bacteria in the absence of COPD or pneumonia; viral infection predominates in a large prospective UK sample,” *Journal of Infection*, vol. 69, no. 5, pp. 507–515, Nov. 2014, doi: 10.1016/j.jinf.2014.07.023.

[80] P. Wongsurakiat, S. Sunhapanit, and N. Muangman, “Bacterial Coinfection and Superinfection in Respiratory Syncytial Virus-Associated Acute Respiratory Illness: Prevalence, Pathogens, Initial Antibiotic-Prescribing Patterns and Outcomes,” *Trop Med Infect Dis*, vol. 8, no. 3, Mar. 2023, doi: 10.3390/tropicalmed8030148.

[81] M. D. Zilberbeg, I. Khan, and A. F. Shorr, “Respiratory Viruses in Nosocomial Pneumonia: An Evolving Paradigm,” Aug. 01, 2023, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/v15081676.

[82] P. Manohar, B. Loh, R. Nachimuthu, X. Hua, S. C. Welburn, and S. Leptihn, “Secondary Bacterial Infections in Patients With Viral Pneumonia,” Aug. 05, 2020, *Frontiers Media S.A.* doi: 10.3389/fmed.2020.00420.

[83] C. B. Wahl *et al.*, “National, regional, and state-level pneumonia and severe pneumonia morbidity in children in India: modelled estimates for 2000 and 2015,” 2020. [Online]. Available: https://www.view-hub.org

[84] A. H. Morice, “Correlation and causality: a COVID-19 conundrum,” Oct. 01, 2020, *NLM (Medline)*. doi: 10.1183/13993003.03174-2020.

[85] F. Checchi and L. Roberts, “Interpreting and using mortality data in humanitarian emergencies- A primer for non-epidemiologists,” *Humanitarian Practice  Network*, London, Sep. 2005. [Online]. Available: www.odihpn.org

[86] D. Anorval, “Symptoms and sites of pain experienced by AIDS patients.”

[87] D. Law’, C. B. Moore, H. M. Wardle, L. A. Ganguli, M. G. L. Keaney, and D. W. Denning^, “High prevalence of antifungal resistance in Candida spp. from patients with AIDS,” 1994. [Online]. Available: http://jac.oxfordjournals.org/

[88] K. Arges *et al.*, “The Project Baseline Health Study: a step towards a broader mission to map human health,” Dec. 01, 2020, *Nature Research*. doi: 10.1038/s41746-020-0290-y.

[89] S. A. Yimer *et al.*, “Rapid diagnostic test: a critical need for outbreak preparedness and response for high priority pathogens,” *BMJ Glob Health*, vol. 9, no. 4, Apr. 2024, doi: 10.1136/bmjgh-2023-014386.

[90] M. J. Mina and K. G. Andersen, “COVID-19 testing: One size does not fit all,” Jan. 08, 2021, *American Association for the Advancement of Science*. doi: 10.1126/science.abe9187.

[91] M. Chaturvedi *et al.*, “A unified framework for diagnostic test development and evaluation during outbreaks of emerging infections,” *Communications Medicine*, vol. 4, no. 1, p. 263, Dec. 2024, doi: 10.1038/s43856-024-00691-9.

[92] A. Ceci *et al.*, “Development and implementation of a scalable and versatile test for COVID-19 diagnostics in rural communities,” *Nat Commun*, vol. 12, no. 1, Dec. 2021, doi: 10.1038/s41467-021-24552-4.

[93] S. Pandey, A. Poudel, D. Karki, and J. Thapa, “Diagnostic accuracy of antigen-detection rapid diagnostic tests for diagnosis of COVID-19 in low-and middle-income countries: A systematic review and meta-analysis,” *PLOS Global Public Health*, vol. 2, no. 4, Apr. 2022, doi: 10.1371/journal.pgph.0000358.

[94] F. Chirico *et al.*, “Efficiency rating of SG Diagnostics COVID-19 antigen rapid test kit,” *Future Virol*, vol. 18, no. 6, pp. 343–348, Apr. 2023, doi: 10.2217/fvl-2021-0210.

[95] S. Katzenschlager *et al.*, “Comparing SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing/self-sampling with molecular and professional-use tests: a systematic review and meta-analysis,” *Sci Rep*, vol. 13, no. 1, Dec. 2023, doi: 10.1038/s41598-023-48892-x.

[96] T. Trenti, “Synergy between point-of-care testing and laboratory consolidations,” *The Journal of the International Federation of Clinical Chemistry and Laboratory medicine*, pp. 328–336, Accessed: Feb. 11, 2025. [Online]. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC8592627/pdf/ejifcc-32-328.pdf

[97] C. Daniel *et al.*, “Cross border semantic interoperability for clinical research: the EHR4CR semantic resources and services.” [Online]. Available: http://www.ehr4cr.eu/

[98] G. Zanello, C. H. Chan, S. Parker, D. Julkowska, and D. A. Pearce, “Fostering the international interoperability of clinical research networks to tackle undiagnosed and under-researched rare diseases,” *Front Med (Lausanne)*, vol. 11, 2024, doi: 10.3389/fmed.2024.1415963.