ISSN 2055-0286
Advances in Social Sciences Research Journal; Vol. 13 No. 11 (2026) (388-409)
https://doi.org/10.14738/assrj.1311.12732

Viral Pathogens as Global Health Threats: Review of Transmissibility, Lethality, and Pandemic Potential

Jonathan A. Coffman[1], Franklin Garcia-Godoy[2], Peter E. Murray[3]

1. Baptist Health Sciences University, Memphis, TN 38104, USA
2. University of Tennessee Health Science Center, College of Dentistry, Memphis, TN 38103, USA
3. 490 Post St, Ste 500 PMB 2045, San Francisco, CA 94102, USA

Abstract: Viral pathogens vary substantially in their transmissibility, lethality, and potential to cause widespread epidemics or pandemics. Measles, for example, is exceptionally contagious but has relatively low case fatality in populations with access to modern medical care. Conversely, rabies, Nipah virus, Ebola virus, and Marburg virus can cause severe disease with high case fatality rates but generally exhibit limited sustained human-to-human transmission. The greatest global threats, therefore, are not necessarily the most contagious or lethal viruses, but those that combine efficient transmission, substantial clinical severity, zoonotic reservoirs, evolutionary adaptability, and limited preventive or therapeutic options. The COVID-19 pandemic illustrated this convergence of risk factors, demonstrating how efficient transmission, including presymptomatic and asymptomatic spread, coupled with clinically significant disease can produce devastating global consequences. Influenza A viruses remain a major pandemic concern because of their extensive animal reservoirs, capacity for antigenic evolution, and established history of human pandemics. Highly pathogenic avian influenza A(H5N1) is particularly concerning given the high case fatality observed among confirmed human cases, although sustained human-to-human transmission has not been established. In contrast, henipaviruses and filoviruses pose substantial clinical threats because of their high lethality, despite comparatively limited transmissibility. This review critically examines major viral threats through three interconnected determinants of global health risk: transmissibility, infection fatality risk, and the biological and epidemiological factors governing their epidemic and pandemic potential.

Keywords: emerging viruses, pandemic, transmissibility, case fatality rate, influenza, H5N1, SARS-CoV-2, Nipah virus, Ebola virus, Marburg virus, measles, viral hemorrhagic fever

INTRODUCTION

The public health significance of a viral pathogen cannot be inferred from lethality alone. The pandemic impact emerges from the interaction of human transmissibility, disease severity, population susceptibility, and the effectiveness of available countermeasures.

Conceptually, population-level risk can be expressed as: **Population health threat ∝ transmission potential × probability of severe disease or death × population susceptibility × epidemic duration × limitations of disease control.**

This framework is illustrative rather than a validated mathematical model. Its determinants include incubation and infectious periods, presymptomatic or asymptomatic transmission, environmental stability, zoonotic reservoirs, viral evolution, preexisting immunity, vaccine and antiviral effectiveness, healthcare capacity, and public health surveillance.[1,2]

Recognizing these interacting determinants, the World Health Organization (WHO) has prioritized pathogens with epidemic potential and insufficient medical countermeasures, including Ebola and Marburg viruses, Nipah virus, Lassa virus, Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus, and the hypothetical *Disease X*, representing an as-yet-unknown pathogen capable of causing a serious international epidemic.[3] WHO has subsequently expanded its preparedness strategy beyond individual pathogens to encompass entire viral families, reflecting the importance of anticipating both known and emerging threats.[4]

Accordingly, evaluating viral threats requires distinguishing three fundamental dimensions: (1) transmissibility, (2) the probability of death following infection, and (3) the combined capacity to produce widespread disease and mortality. These dimensions provide a clinically and epidemiologically grounded framework for comparing existing viral pathogens and assessing their future epidemic and pandemic potential.

TRANSMISSIBILITY VERSUS LETHALITY

Transmissibility and lethality are distinct but interdependent determinants of viral epidemic and pandemic potential. Transmissibility is commonly characterized by the *basic reproduction number* (R_0), defined as the average number of secondary infections generated by an infected individual in a fully susceptible population under specified conditions. An R_0 greater than 1 indicates the potential for sustained transmission, whereas an R_0 below 1 generally predicts declining transmission.

However, R_0 is not a fixed biological property of a virus; it varies with contact patterns, population density, environmental conditions, and viral characteristics. The *effective reproduction number* (R_t) further reflects changes in population immunity, behavior, and public health interventions over time.[1,5]

Lethality is commonly quantified using the case fatality ratio (CFR):

$$\text{CFR} = \frac{\text{Deaths among identified cases}}{\text{Total identified cases}} \times 100$$

However, CFR estimates are influenced by surveillance intensity, diagnostic capacity, case definitions, disease severity, healthcare availability, and delays between diagnosis and death. Underascertainment of mild or asymptomatic infections may substantially overestimate lethality, whereas incomplete mortality reporting may underestimate it. The “infection fatality ratio (IFR)”, which includes all infected individuals regardless of clinical recognition, provides a more comprehensive measure of mortality risk but is often difficult to estimate reliably, particularly during emerging outbreaks.[6,7]

These limitations are especially relevant to zoonotic pathogens such as highly pathogenic avian influenza A(H5N1), for which surveillance has historically concentrated on severe, clinically recognized infections. Consequently, the high CFR reported among confirmed human cases should not be interpreted as the mortality risk associated with all infections.[8] Accordingly, comparisons of viral transmissibility and lethality must account for differences in surveillance, population characteristics, healthcare resources, and

epidemiological context. Neither R_0 nor CFR alone adequately predicts pandemic impact; the greatest population-level danger arises when sustained transmission coincides with substantial clinical severity and limited opportunities for effective control.[1,6]

MEASLES: EXTREME VIRAL CONTAGIOUSNESS

Measles virus is among the most transmissible human pathogens, with an estimated basic reproduction number (R_0) of 12 to 18 in historically susceptible populations, although estimates vary substantially across epidemiological settings.[9] Its exceptional contagiousness results from efficient airborne transmission, infectiousness before the characteristic rash develops, and the ability of virus-containing respiratory particles to remain suspended in the air for up to two hours. Consequently, even brief exposure in inadequately ventilated environments can result in infection among susceptible individuals.[10]

Despite its extraordinary transmissibility, measles has substantially lower-case fatality than highly lethal viral pathogens such as Ebola and Marburg viruses. Nevertheless, measles can cause severe pneumonia, encephalitis, immunosuppression, and death, particularly among young children, malnourished individuals, and immunocompromised patients. Its clinical severity varies considerably with age, nutritional status, healthcare access, and underlying population vulnerability.[11,12]

Widespread vaccination has fundamentally altered the epidemiology of measles, transforming a historically ubiquitous childhood infection into a largely preventable disease. However, because of its high transmissibility, sustained interruption of transmission generally requires population immunity approaching 95%.[13] Declining vaccination coverage can therefore rapidly restore conditions favorable to outbreaks, including in countries where endemic transmission was previously eliminated. Measles exemplifies the profound population-level consequences of extreme transmissibility despite comparatively modest individual mortality risk. Its continued resurgence underscores a central principle of pandemic preparedness: effective medical countermeasures reduce infectious disease threats only when sufficiently accessible, accepted, and consistently implemented.[13,14]

The accompanying figures illustrate the interplay among viral transmissibility, lethality, zoonotic reservoirs, evolutionary adaptability, and pandemic potential. Comparisons of major viral pathogens demonstrate how these factors influence clinical severity, sustained human transmission, and population-level risk. The figures also highlight the roles of cross-species transmission, antigenic evolution, host susceptibility, and medical countermeasures in viral emergence and spread, emphasizing the importance of integrated surveillance, prevention, and pandemic preparedness (Figure 1).

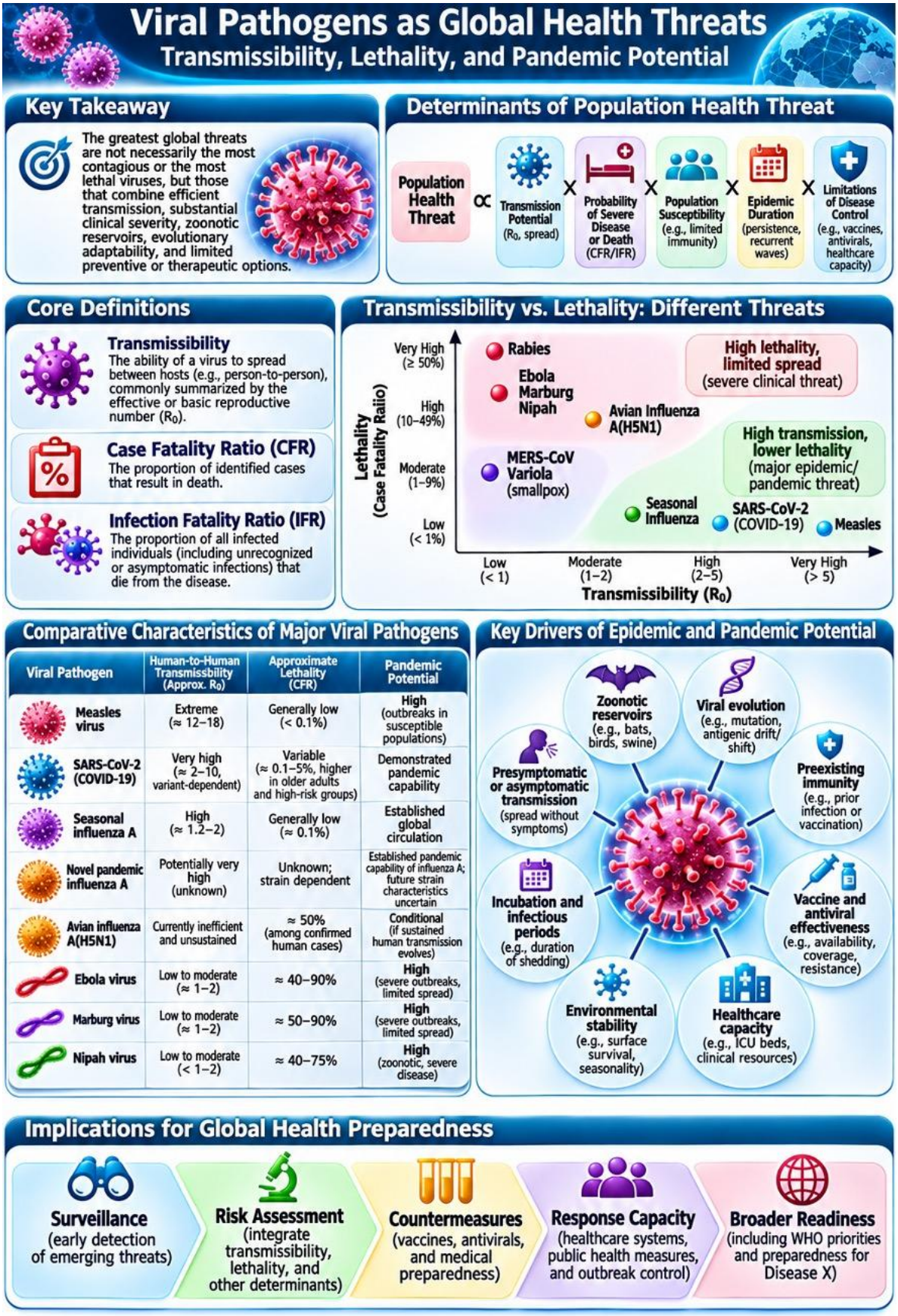
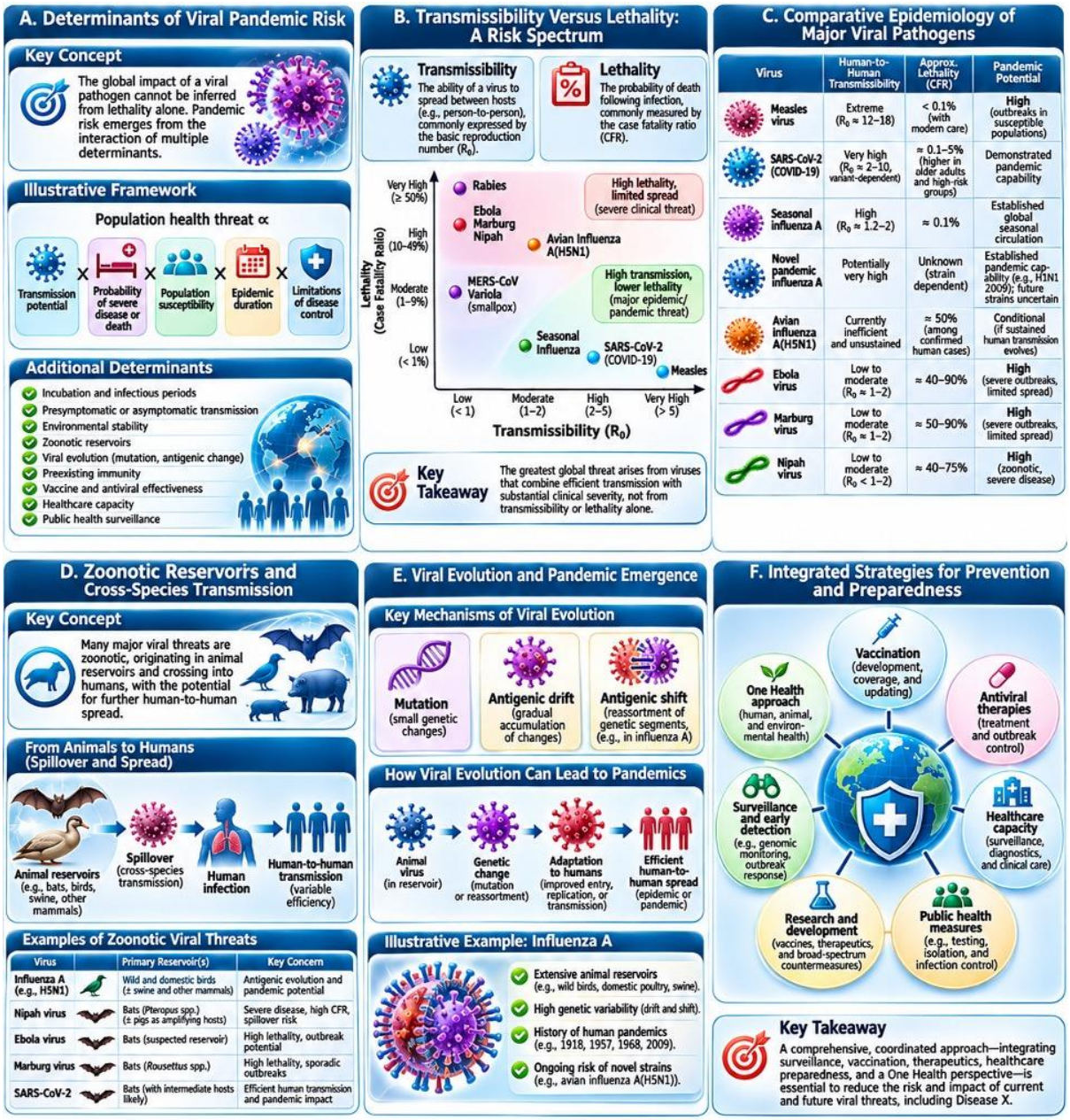

Viral Pathogens as Global Health Threats
Transmissibility, Lethality, and Pandemic Potential
Key Takeaway
The greatest global threats are not necessarily the most contagious or the most lethal viruses, but those that combine efficient transmission, substantial clinical severity, zoonotic reservoirs, evolutionary adaptability, and limited preventive or therapeutic options.
Determinants of Population Health Threat
Population Health Threat
∝
Transmission Potential (R0, spread)
X
Probability of Severe Disease or Death (CFR/IFR)
X
Population Susceptibility (e.g., limited immunity)
X
Epidemic Duration (persistence, recurrent waves)
X
Limitations of Disease Control (e.g., vaccines, antivirals, healthcare capacity)
Core Definitions
Transmissibility
The ability of a virus to spread between hosts (e.g., person-to-person), commonly summarized by the effective or basic reproductive number (R0).
Case Fatality Ratio (CFR)
The proportion of identified cases that result in death.
Infection Fatality Ratio (IFR)
The proportion of all infected individuals (including unrecognized or asymptomatic infections) that die from the disease.
Transmissibility vs. Lethality: Different Threats
Lethality (Case Fatality Raiio)
Very High (≥ 50%)
High (10–49%)
Moderate (1–9%)
Low (< 1%)
Rabies
Ebola
Marburg
Nipah
Avian Influenza A(H5N1)
High lethality, limited spread (severe clinical threat)
MERS-CoV
Variola (smallpox)
High transmission, lower lethality (major epidemic/ pandemic threat)
Seasonal Influenza
SARS-CoV-2 (COVID-19)
Measles
Low (< 1)
Moderate (1–2)
High (2–5)
Very High (> 5)
Transmissibility (R0)
Comparative Characteristics of Major Viral Pathogens
Viral Pathogen | Human-to-Human Transmissbility (Approx. R0) | Approximate Lethality (CFR) | Pandemic Potential
Measles virus | Extreme (≈ 12–18) | Generally low (< 0.1%) | High (outbreaks in susceptible populations)
SARS-CoV-2 (COVID-19) | Very high (≈ 2–10, variant-dependent) | Variable (≈ 0.1–5%, higher in older adults and high-risk groups) | Demonstrated pandemic capability
Seasonal influenza A | High (≈ 1.2–2) | Generally low (≈ 0.1%) | Established global circulation
Novel pandemic influenza A | Potentially very high (unknown) | Unknown; strain dependent | Established pandemic capability of influenza A; future strain characteristics uncertain
Avian influenza A(H5N1) | Currently inefficient and unsustained | ≈ 50% (among confirmed human cases) | Conditional (if sustained human transmission evolves)
Ebola virus | Low to moderate (≈ 1–2) | ≈ 40–90% | High (severe outbreaks, limited spread)
Marburg virus | Low to moderate (≈ 1–2) | ≈ 50–90% | High (severe outbreaks, limited spread)
Nipah virus | Low to moderate (< 1–2) | ≈ 40–75% | High (zoonotic, severe disease)
Key Drivers of Epidemic and Pandemic Potential
Zoonotic reservoirs (e.g., bats, birds, swine)
Viral evolution (e.g., mutation, antigenic drift/ shift)
Presymptomatic or asymptomatic transmission (spread without symptoms)
Preexisting immunity (e.g., prior infection or vaccination)
Incubation and infectious periods (e.g., duration of shedding)
Vaccine and antiviral effectiveness (e.g., availability, coverage, resistance)
Environmental stability (e.g., surface survival, seasonality)
Healthcare capacity (e.g., ICU beds, clinical resources)
Implications for Global Health Preparedness
Surveillance (early detection of emerging threats)
Risk Assessment (integrate transmissibility, lethality, and other determinants)
Countermeasures (vaccines, antivirals, and medical preparedness)
Response Capacity (healthcare systems, public health measures, and outbreak control)
Broader Readiness (including WHO priorities and preparedness for Disease X)

Figure 1



INFLUENZA A: PERHAPS THE MOST PERSISTENT PANDEMIC THREAT

Influenza A viruses represent one of the most enduring pandemic threats because of their efficient respiratory transmission, extensive animal reservoirs, remarkable evolutionary adaptability, and established history of causing global pandemics. Seasonal influenza alone accounts for approximately one billion infections annually, including 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths worldwide.[15]

The greater pandemic concern arises from influenza A's capacity for genetic evolution and cross-species transmission. Its segmented RNA genome permits *antigenic shift through reassortment*, while accumulated mutations produce *antigenic drift*, facilitating immune escape and periodic emergence of novel variants. Extensive circulation among wild birds, domestic poultry, and mammalian hosts creates opportunities for zoonotic transmission and viral adaptation.[16,17] The pandemics of 1918, 1957, 1968, and 2009 demonstrate the recurring ability of influenza A viruses to acquire efficient human

transmissibility and spread globally, sometimes with devastating consequences.[18] This concern is reinforced by expert assessments of future pandemic risks. In an international survey of infectious disease specialists, approximately 79% of respondents identified influenza viruses among the pathogens of greatest pandemic concern.[19] Although expert opinion cannot establish the probability of a future pandemic, it underscores the scientific importance attributed to influenza's epidemiological and evolutionary characteristics.

Influenza A's distinctive threat lies in the convergence of sustained animal circulation, genetic plasticity, respiratory transmissibility, and demonstrated pandemic potential. Unlike pathogens whose emergence depends on rare spillover events, influenza A viruses circulate continuously across multiple host species, creating recurring opportunities for the emergence of antigenically novel strains. Consequently, influenza remains a persistent global health threat requiring sustained surveillance, adaptable vaccination strategies, and coordinated pandemic preparedness.[16,17]

H5N1 AVIAN INFLUENZA: HIGH LETHALITY WITHOUT EFFICIENT HUMAN TRANSMISSION

Highly pathogenic avian influenza A(H5N1) warrants particular concern because of its substantial clinical severity in historically documented human infections, extensive animal reservoirs, and potential for evolutionary adaptation. Since 1997, more than 900 laboratory-confirmed human cases have been reported worldwide, with approximately half resulting in death. However, this observed case fatality proportion should not be equated with the infection fatality ratio, as surveillance has disproportionately identified severely ill patients while potentially missing mild or asymptomatic infections.[20]

Despite its pathogenic potential, H5N1 has not demonstrated efficient, sustained human-to-human transmission, a critical epidemiological barrier to pandemic emergence. Human infections have occurred predominantly following exposure to infected animals or contaminated environments, with limited person-to-person transmission reported under exceptional circumstances.[21] Thus, the current threat is characterized by substantial pathogenicity, widespread animal circulation, and recurrent zoonotic spillover without established sustained transmission among humans.

The principal pandemic concern is the possibility that an H5 influenza lineage could acquire efficient human respiratory transmissibility through genetic adaptation or reassortment. Such an event, particularly in a population with limited preexisting immunity, could fundamentally alter its epidemiological impact. However, increased transmissibility would not necessarily preserve the high case fatality observed among historically confirmed H5N1 infections, because viral pathogenicity, host adaptation, and disease severity are influenced by distinct but interacting biological mechanisms.[16,22]

Accordingly, H5N1 illustrates the distinction between a pathogen's current clinical lethality and its potential future pandemic impact. Its greatest global significance lies not solely in the severity of recognized human infections, but in the possibility of evolutionary changes enabling sustained human transmission while maintaining clinically significant virulence. This uncertainty underscores the importance of integrated animal and human surveillance, rapid detection of zoonotic infections, and continued development of effective vaccines and antiviral countermeasures.[20,21]

SARS-COV-2: THE PANDEMIC CONSEQUENCES OF HIGH TRANSMISSIBILITY AND CLINICALLY SIGNIFICANT LETHALITY

SARS-CoV-2 provides a compelling modern demonstration that a high transmissibility combined with clinically significant, even if comparatively modest, infection fatality can produce catastrophic population-level mortality. Unlike highly lethal pathogens with limited human-to-human transmission, SARS-CoV-2 achieved rapid global dissemination through efficient respiratory transmission, substantial presymptomatic and asymptomatic spread, and initially widespread population susceptibility.[23,24] These characteristics enabled extensive transmission before infected individuals could be identified and isolated, substantially complicating conventional containment strategies.

The resulting pandemic demonstrated how a virus causing severe disease in a minority of infected individuals can nevertheless overwhelm healthcare systems when infections occur on an extraordinary scale. COVID-19 mortality was further amplified by advanced age, underlying comorbidities, healthcare disparities, and limitations in clinical capacity during epidemic surges. Although infection fatality risk varied considerably across populations and pandemic phases, the cumulative consequences were profound. The World Health Organization estimated approximately 14.9 million excess deaths globally during 2020 and 2021, illustrating the pandemic's direct and indirect mortality burden.[25]

The emergence of successive SARS-CoV-2 variants further demonstrated how viral evolution can alter transmissibility, immune escape, and disease burden, while vaccination, prior infection, and improved clinical management substantially modify population vulnerability.[26] Consequently, pandemic severity is not determined by viral characteristics alone but evolves through interactions among pathogen biology, host immunity, healthcare capacity, and public health responses.

SARS-CoV-2 illustrates a central principle of pandemic risk: a highly transmissible respiratory virus need not exhibit extreme individual lethality to cause unprecedented global morbidity and mortality. Its emergence and continued evolution underscore the importance of early detection, rapid countermeasure development, and sustained preparedness for novel respiratory pathogens.[3,4]

MERS-COV: HIGH LETHALITY CONSTRAINED BY LIMITED HUMAN TRANSMISSION

Middle East respiratory syndrome coronavirus (MERS-CoV) illustrates how substantial clinical lethality can coexist with limited pandemic potential under prevailing transmission conditions. Since its identification in 2012, MERS-CoV has caused severe respiratory disease, frequently complicated by pneumonia, acute respiratory distress syndrome, and multiorgan dysfunction, particularly among older adults and individuals with underlying comorbidities. Approximately 35% of laboratory-confirmed cases have resulted in death, although this observed case fatality ratio likely overestimates the infection fatality risk because mild and asymptomatic infections may remain undetected.[27]

Unlike SARS-CoV-2, MERS-CoV has not established sustained, efficient community transmission. Most human infections have resulted from zoonotic exposure to infected dromedary camels or secondary transmission, particularly within healthcare facilities, where substantial outbreaks have occurred.[28] Although nosocomial transmission demonstrates the virus's capacity for significant human-to-human spread under favorable

conditions, its overall transmission efficiency has remained insufficient to sustain widespread community epidemics.[29]

Nevertheless, MERS-CoV remains a significant emerging infectious disease threat because of its clinical severity, persistent animal reservoir, and potential for further viral adaptation. The emergence of severe acute respiratory syndrome (SARS) in 2002, MERS in 2012, and COVID-19 in 2019 demonstrates the repeated capacity of zoonotic coronaviruses to cross species barriers and cause serious human disease.[30] Recognizing this recurring threat, the World Health Organization prioritizes coronavirus groups, including sarbecoviruses and merbecoviruses, within its pathogen-family preparedness framework.[4]

MERS-CoV exemplifies the epidemiological distinction between individual lethality and population-level pandemic risk. Although its observed case fatality substantially exceeds that of COVID-19, limited sustained human transmission has constrained its global impact. Its continued circulation nevertheless underscores the importance of zoonotic surveillance, infection prevention in healthcare settings, and preparedness for emerging coronaviruses with potentially altered transmission characteristics.

NIPAH VIRUS: HIGH LETHALITY AND EMERGING PANDEMIC POTENTIAL

Nipah virus (NiV), a zoonotic henipavirus, represents a particularly concerning emerging infectious disease threat because of its exceptionally high case fatality, capacity for human-to-human transmission, and absence of licensed vaccines or specific antiviral therapies. Reported case fatality ratios range from approximately 40% to 75%, varying with outbreak characteristics, surveillance practices, and clinical management. Human infection can cause rapidly progressive encephalitis, severe respiratory disease, and multiorgan complications, with neurological sequelae reported among survivors.[31,32] Fruit bats of the genus *Pteropus* serve as the natural reservoir, with human infections arising through contact with infected animals, consumption of contaminated raw date palm sap or fruit, and secondary transmission between humans.[31,32] Recurrent outbreaks in Bangladesh and India have demonstrated the capacity for person-to-person spread, particularly through close contact with infected individuals and their bodily fluids. Respiratory involvement may further facilitate transmission, although sustained community spread has remained limited.[33,34]

Nipah virus combines several characteristics associated with emerging pandemic threats: persistent zoonotic reservoirs, recurrent spillover, severe neurological and respiratory manifestations, high observed lethality, and documented human-to-human transmission. Nevertheless, its comparatively inefficient transmission between humans has thus far restricted outbreaks primarily to localized or regional settings. The absence of licensed vaccines and virus-specific therapeutics further complicates outbreak control, although investigational vaccines and monoclonal antibodies are under development.[31,35]

Nipah virus illustrates the potentially dangerous convergence of extreme clinical severity and established, but currently limited, human transmissibility. Although its present epidemiology does not support efficient pandemic-scale spread, evolutionary changes that substantially enhance sustained respiratory transmission could fundamentally alter its global threat profile. Its high lethality, recurrent zoonotic emergence, and limited medical countermeasures justify continued prioritization in global surveillance, research, and pandemic preparedness.[4,35]

EBOLA VIRUS: EXTREME LETHALITY BUT COMPARATIVELY CONSTRAINED TRANSMISSION

Ebola virus disease (EVD) represents one of the most severe emerging viral infections, characterized by systemic inflammation, vascular dysfunction, multiorgan injury, and potentially fatal shock. The World Health Organization reports an average case fatality ratio of approximately 50%, with mortality ranging from 25% to 90% across historical outbreaks, reflecting differences in viral species, clinical management, and healthcare capacity.[36] Despite this exceptional lethality, Ebola viruses generally exhibit substantially lower human-to-human transmissibility than measles, influenza, or SARS-CoV-2.

Transmission occurs primarily through direct contact with blood, bodily fluids, or contaminated materials from infected symptomatic individuals or deceased patients. Unlike respiratory viruses capable of substantial presymptomatic transmission, Ebola virus transmission is closely associated with symptomatic illness, creating opportunities for early case identification, isolation, contact tracing, infection prevention, and safe burial practices.[1,36] The availability of effective vaccines and monoclonal antibody therapies against *Zaire ebolavirus* has further improved outbreak prevention and clinical outcomes, although these countermeasures do not provide equivalent protection against all ebolaviruses.[37,38]

Nevertheless, the 2014 to 2016 West African Ebola epidemic, which caused more than 28,000 reported cases and 11,000 deaths, demonstrated the devastating consequences of uncontrolled transmission in settings with fragile healthcare infrastructure, delayed surveillance, inadequate infection control, and limited community engagement.[39] This epidemic established that comparatively inefficient transmission does not preclude extensive regional spread when public health systems are overwhelmed.

Ebola illustrates the distinction between extreme individual lethality and pandemic-scale transmission potential. Although its transmission characteristics provide opportunities for effective containment, delayed recognition and inadequate public health responses can transform localized outbreaks into major humanitarian emergencies. Its continuing threat therefore reflects not only viral pathogenicity but also the capacity of healthcare and public health systems to interrupt transmission before widespread dissemination.[1,36]

MARBURG VIRUS: EXTREME LETHALITY WITH LIMITED HUMAN TRANSMISSIBILITY

Marburg virus, a member of the *Filoviridae* family closely related to Ebola virus, causes severe viral hemorrhagic fever characterized by systemic inflammation, vascular dysfunction, coagulopathy, multiorgan failure, and potentially fatal shock. The World Health Organization reports an average case fatality ratio of approximately 50%, with observed mortality ranging from 24% to 88% across historical outbreaks, depending on clinical management, outbreak characteristics, and healthcare resources.[40] These findings establish Marburg virus as one of the most lethal recognized human viral pathogens.

Egyptian fruit bats (*Rousettus aegyptiacus*) constitute the principal natural reservoir, with zoonotic transmission occurring through exposure to infected bats or contaminated environments. Subsequent human-to-human transmission occurs primarily through direct contact with infectious blood, bodily fluids, or contaminated materials, particularly in households, healthcare facilities, and during funeral practices.[40,41] Unlike highly

transmissible respiratory viruses, Marburg virus has not demonstrated efficient sustained airborne transmission between humans, limiting its potential for rapid community-wide dissemination under prevailing epidemiological conditions.

Nevertheless, Marburg virus remains a substantial emerging infectious disease threat because of its exceptional clinical severity, recurrent zoonotic introductions, potential for healthcare-associated amplification, and limited medical countermeasures. Although investigational vaccines and therapeutics are under development, no licensed vaccine or virus-specific antiviral treatment is currently available for routine clinical use.[40,42] Consequently, outbreak control depends heavily on rapid diagnosis, patient isolation, rigorous infection prevention, contact tracing, and supportive clinical management.

Marburg virus exemplifies the extreme-lethality end of the viral threat spectrum: capable of devastating individual outcomes and severe localized outbreaks but constrained by transmission mechanisms that have not supported sustained global dissemination. Its continued emergence reinforces the importance of surveillance at human-animal interfaces, strengthened healthcare infection control, and accelerated development of effective medical countermeasures.[40,41]

RABIES: NEAR-UNIVERSAL FATALITY AFTER CLINICAL ONSET

Rabies represents the extreme of individual viral lethality. Once clinical disease develops, rabies is almost invariably fatal, with only a small number of documented survivors, many experiencing severe neurological sequelae.[43]

Following inoculation through infected saliva, rabies virus invades the peripheral nervous system and progresses toward the central nervous system, producing acute, progressive encephalitis characterized by neurological dysfunction, autonomic instability, and ultimately cardiorespiratory failure.[44]

Despite its extraordinary lethality, rabies has negligible potential for sustained human-to-human epidemic transmission. Human infections occur predominantly following bites or other exposures to infected mammals, particularly dogs in endemic regions. Although transmission through organ transplantation has been documented, ordinary interpersonal contact does not propagate infection.[43,44] Consequently, rabies remains a major zoonotic public health threat rather than a conventional pandemic threat, causing an estimated 59,000 human deaths annually worldwide, predominantly in regions with inadequate access to animal vaccination and timely medical care.[45] Importantly, rabies is preventable despite its near-universal fatality after symptom onset. Prompt wound cleansing and appropriate post-exposure prophylaxis (PEP), including rabies vaccination and rabies immune globulin when indicated, are highly effective in preventing clinical disease when administered before symptom onset.[46] This sharp contrast between preventability and clinical lethality underscores the critical importance of early intervention.

Rabies and measles illustrate opposite extremes of the transmissibility-lethality spectrum: rabies approaches universal fatality after clinical onset but lacks sustained human-to-human transmission, whereas measles spreads exceptionally efficiently yet has substantially lower-case fatality. Their contrasting epidemiology demonstrates why individual mortality risk cannot independently determine a pathogen's population-level epidemic or pandemic potential.

SMALLPOX: THE HISTORICAL BENCHMARK FOR HIGH TRANSMISSIBILITY AND LETHALITY

Smallpox, caused by variola virus, provides a compelling historical example of the devastating consequences of combining efficient human-to-human transmission with substantial clinical lethality. Unlike highly lethal zoonotic pathogens whose spread is constrained by limited interpersonal transmission, variola virus circulated exclusively among humans and sustained recurrent epidemics across populations. Historically, ordinary smallpox (*variola major*) produced case fatality ratios approaching 30%, with particularly severe outcomes among immunologically susceptible individuals.[47,48]

Transmission occurred predominantly through close respiratory exposure, particularly during prolonged face-to-face contact, and through contact with infectious lesions or contaminated materials. Although less contagious than measles, smallpox possessed sufficient transmissibility to sustain extensive epidemics, especially in densely populated communities lacking preexisting immunity.[48] Its combination of substantial lethality, sustained human transmission, and widespread susceptibility made smallpox one of the most consequential infectious diseases in human history.

The global eradication of smallpox demonstrates that even highly consequential viral threats can be eliminated through effective vaccination, surveillance, and coordinated public health interventions. The last naturally acquired case occurred in Somalia in 1977, and the World Health Assembly formally declared global eradication in 1980.[47,49] This achievement was facilitated by the absence of a nonhuman reservoir, effective vaccination, and recognizable clinical manifestations that supported case detection and containment.

Smallpox establishes a historical benchmark for the catastrophic potential of viruses combining sustained human transmissibility with high case fatality. Its eradication illustrates the transformative effectiveness of coordinated prevention, while its historical burden underscores the importance of identifying emerging pathogens capable of achieving a similarly dangerous combination of transmission efficiency and clinical severity.

COMPARATIVE ASSESSMENT OF VIRAL TRANSMISSIBILITY, LETHALITY, AND PANDEMIC POTENTIAL

A comparative assessment must distinguish the danger posed to an infected patient from the capacity of a pathogen to generate widespread disease. Human transmission, clinical severity, host immunity, animal reservoirs, viral adaptability, and access to countermeasures jointly shape population-level impact.

The comparison reveals three distinct patterns: measles exemplifies extreme transmissibility; rabies, Nipah, Ebola, and Marburg illustrate exceptional clinical lethality with constrained transmission; and SARS-CoV-2 and influenza A demonstrate the profound population-level consequences of efficient respiratory spread. Smallpox provides the historical example of substantial transmissibility combined with high mortality. Collectively, these findings reinforce that the greatest pandemic danger arises not from lethality or contagiousness in isolation, but from their convergence in a susceptible population, particularly when effective countermeasures are unavailable or insufficiently deployed.

COMPARATIVE PATTERNS OF CLINICAL LETHALITY

Ranking pathogens by observed fatality highlights clinical severity rather than epidemic reach. Rabies approaches universal fatality after symptom onset, whereas Marburg, Ebola, Nipah, and historically confirmed H5N1 infections have also exhibited high case fatality.[43,44]

Marburg virus, Ebola virus, Nipah virus, and highly pathogenic avian influenza A(H5N1) constitute a second group characterized by exceptionally high observed case fatality. Historical outbreaks have demonstrated mortality approaching 90% for Marburg and Ebola virus diseases, while Nipah virus case fatality estimates range from 40% to 75%. Approximately half of historically confirmed human H5N1 infections have resulted in death, although preferential detection of severe cases likely overestimates the mortality risk across all infections.[20,31,36,40]

MERS-CoV and variola major represent another high-lethality category, with historically reported case fatality ratios of approximately 35% and 30%, respectively.[27,48] In contrast, measles, seasonal influenza, and SARS-CoV-2 generally exhibit lower individual mortality risks, although these vary substantially with age, immunity, underlying disease, and access to medical care.[11,15,25]

The comparative characteristics of major viral pathogens are summarized in the table, highlighting the distinction between individual clinical lethality and population-level pandemic risk. Measles, SARS-CoV-2, and influenza A demonstrate the substantial public health consequences of efficient human-to-human transmission, whereas rabies, Nipah, Ebola, Marburg, and H5N1 exhibit greater clinical lethality but more limited sustained transmission. Smallpox provides a historical example of the devastating combination of high transmissibility and substantial mortality. Collectively, these comparisons demonstrate that pandemic potential depends not on lethality or transmissibility alone, but on their interaction with population susceptibility, viral evolution, zoonotic reservoirs, and the availability of effective preventive and therapeutic measures. A comparative table of the epidemiological characteristics and pandemic threat profiles of major viral pathogens is shown in Table 1 below.

These comparisons require important methodological caution, because the reported case fatality ratios reflect heterogeneous surveillance systems, case definitions, clinical populations, and treatment conditions. Furthermore, fatality after symptomatic disease, fatality among laboratory-confirmed cases, and fatality among all infected individuals are distinct epidemiological measures and cannot be treated as interchangeable.[6,7]

Ultimately, lethality rankings identify the pathogens most dangerous to an infected individual, not necessarily those capable of causing the greatest population-level mortality. A highly transmissible virus with comparatively low infection fatality may produce substantially more deaths than an exceptionally lethal pathogen whose transmission remains limited.

Thus, individual clinical severity must be interpreted alongside transmission dynamics, population susceptibility, and the effectiveness of available preventive and therapeutic interventions.

Table 1: Comparative Epidemiological Characteristics and Pandemic Threat Profiles of Major Viral Pathogens

Viral pathogen	Human-to-human transmissibility	Approximate lethality	Pandemic potential	Principal public health concern
Measles virus	Extreme	Generally low CFR in settings with advanced medical care	High outbreak potential in susceptible populations; constrained by vaccination	Exceptional contagiousness and immunity gaps
SARS-CoV-2	Very high	Variable; strongly influenced by age, immunity, and healthcare access	Demonstrated pandemic capability	Efficient respiratory transmission and substantial cumulative mortality
Seasonal influenza A	High	Generally low CFR	Established global seasonal circulation	Recurrent epidemics and substantial annual disease burden
Novel pandemic influenza A	Potentially very high	Unknown; strain dependent	Established pandemic capability of influenza A; future strain characteristics uncertain	Antigenic novelty, animal reservoirs, and evolutionary adaptability
Avian influenza A(H5N1)	Currently inefficient and unsustained	~ 50% CFR among confirmed human cases	Conditional on acquisition of sustained human transmissibility	Severe zoonotic disease and potential viral adaptation
MERS-CoV	Limited sustained community transmission; healthcare-associated outbreaks	~ 35% CFR among confirmed cases	Currently constrained; future evolutionary risk uncertain	Severe respiratory disease & persistent zoonotic reservoir
Nipah virus	Limited, with documented person-to-person transmission	40% to 75% CFR	Currently constrained; potentially consequential if transmissibility increases	Severe encephalitis, respiratory disease, & limited countermeasures
Ebola virus	Primarily direct-contact transmission	Approximately 50% average CFR; historically 25% to 90%	Major regional epidemic potential; limited conventional respiratory pandemic potential	Severe outbreaks and healthcare-associated transmission
Marburg virus	Primarily direct-contact transmission	Approximately 50% average CFR; historically 24% to 88%	Major regional epidemic potential; limited conventional respiratory pandemic potential	Extreme clinical severity and limited medical countermeasures
Rabies virus	Negligible sustained human-to-human transmission	Nearly 100% fatality after clinical onset	Negligible conventional pandemic potential	Near-universal fatality of symptomatic disease
Variola virus (smallpox)	Historically high	~ 30% CFR for ordinary variola major	No natural circulation following eradication	Historical demonstration of sustained transmission combined with high lethality

Abbreviations: CFR, (case fatality ratio); MERS-CoV (Middle East respiratory syndrome coronavirus); SARS-CoV-2, (severe acute respiratory syndrome coronavirus-2). Sources: references.[9, 11, 15, 16, 18, 20, 23, 25, 27, 31, 36, 40, 43,47-49]

COMPARATIVE PATTERNS OF HUMAN TRANSMISSION

Ranking pathogens by sustained human-to-human spread yields a different ordering. Measles occupies the extreme of contagiousness, while SARS-CoV-2 and human-adapted influenza A readily propagate through respiratory transmission.[9]

SARS-CoV-2 and human-adapted influenza A viruses constitute another major category of highly transmissible respiratory pathogens. Their capacity for efficient community spread, including transmission before symptoms become clinically apparent, enables extensive dissemination across populations and geographic regions.[16,23,24] Smallpox

historically demonstrated substantial person-to-person transmissibility, sufficient to sustain widespread epidemics before its eradication.[48]

In contrast, MERS-CoV, Nipah virus, Ebola virus, and Marburg virus have exhibited comparatively constrained human transmission. Although these pathogens can cause severe outbreaks, including substantial healthcare-associated and household transmission, their epidemiological characteristics have not supported the sustained, widespread community transmission observed with measles, influenza, or SARS-CoV-2.[29,34,36,40] Highly pathogenic avian influenza A(H5N1) similarly remains limited by the absence of efficient sustained human-to-human transmission, despite its extensive circulation in animal populations.[20,21] Rabies occupies the opposite extreme, as human infections arise overwhelmingly from animal exposures and do not ordinarily generate secondary human cases.[43,44]

Importantly, transmissibility cannot be reduced to a universal numerical ranking because reproduction numbers depend on population susceptibility, contact patterns, viral characteristics, and environmental conditions.[1,5] Nevertheless, the epidemiological distinction is clear: the viruses most likely to cause death following infection are not necessarily those most capable of spreading through human populations. This divergence reinforces the importance of evaluating transmission efficiency and clinical lethality as separate, interacting determinants of epidemic and pandemic risk.

CONVERGENCE OF TRANSMISSIBILITY AND LETHALITY

From a global health perspective, the greatest pandemic threat arises when efficient human-to-human transmission converges with substantial clinical lethality, particularly in populations with limited preexisting immunity and inadequate medical countermeasures. This relationship can be illustrated through a conceptual transmissibility-lethality matrix, recognizing that actual epidemic outcomes depend on additional biological, ecological, and public health determinants.[1,5] The hypothetical emergence of a virus combining measles-like transmissibility with rabies-like fatality would represent an extraordinary biological and public health threat. However, no currently circulating human virus is known to exhibit both characteristics, and such a combination should not be regarded as an inevitable or predictable evolutionary outcome. The mix of viral transmissibility, lethality, and population-Level Threat is shown in Table 2 below.

Table 2: Conceptual Matrix of Viral Transmissibility, Lethality, and Population-Level Threat

Human transmissibility	Lower lethality	Higher lethality
Low	Generally limited epidemic impact, although recurrent infections may create substantial cumulative burden	Rabies, Nipah, Ebola, and Marburg: severe individual outcomes and potentially devastating localized or regional outbreaks
High	Measles and seasonal respiratory viruses: extensive transmission and potentially substantial cumulative morbidity and mortality	Greatest potential for catastrophic pandemics:historical smallpox and hypothetical emerging viruses combining efficient transmission with high infection fatality

Some more plausible pandemic scenarios involve pathogens possessing several mutually reinforcing characteristics: efficient respiratory transmission, substantial presymptomatic or minimally symptomatic spread, an incubation period permitting transmission before detection, limited population immunity, clinically significant infection fatality, and the capacity for continued viral evolution. Persistent animal reservoirs and recurrent zoonotic spillover further increase opportunities for emergence, while inadequate vaccines, therapeutics, surveillance, and healthcare capacity amplify potential consequences.[1,2,16]

SARS-CoV-2 demonstrated how this convergence can produce devastating global mortality without extreme individual lethality, whereas influenza A illustrates how extensive animal reservoirs, antigenic evolution, and established respiratory transmissibility create recurring opportunities for pandemic emergence. [16,18,23,25] Ultimately, the most dangerous pandemic pathogen is not necessarily the virus with the highest case fatality or reproduction number, but one capable of sustaining widespread transmission while causing substantial disease and death in a susceptible population. This interaction, rather than either characteristic in isolation, provides the most meaningful framework for anticipating future pandemic threats and prioritizing global preparedness.

DISEASE X AND THE LIMITS OF PANDEMIC PREDICTION

The next major pandemic threat may arise from a virus not yet recognized as a significant human pathogen. The WHO introduced the concept of "*Disease X*" to acknowledge that a serious international epidemic could emerge from an unknown pathogen, underscoring the inherent limitations of predicting future pandemic agents.[3] This uncertainty reflects the complex and often unpredictable interactions among viral evolution, zoonotic spillover, host susceptibility, environmental change, and human behavior. Although surveillance and genomic analysis can identify emerging risks, neither the identity nor the timing of the next pandemic pathogen can be predicted reliably. Consequently, pandemic preparedness cannot depend exclusively on identifying individual viruses considered most likely to emerge. Recognizing this limitation, WHO expanded its research prioritization framework to encompass 28 viral families and 1,652 pathogens, emphasizing preparedness across pathogen families rather than exclusively targeting a limited list of known threats.[4] This approach promotes the development of prototype vaccines, broadly applicable diagnostic platforms, and adaptable therapeutic strategies that may accelerate responses to newly emerging pathogens.

Disease X therefore represents a fundamental principle of pandemic preparedness: the greatest future threat may originate from a known virus, a previously overlooked member of an established viral family, or an entirely unrecognized human pathogen. Effective preparedness must consequently integrate pathogen-specific surveillance with flexible, broadly applicable medical countermeasures and resilient public health systems capable of responding rapidly to biological threats that cannot yet be anticipated.[3,4] A decision tree for the transmissibility, lethality, and pandemic potential of modern viral pathogenic threats is shown in Figure 2 below.

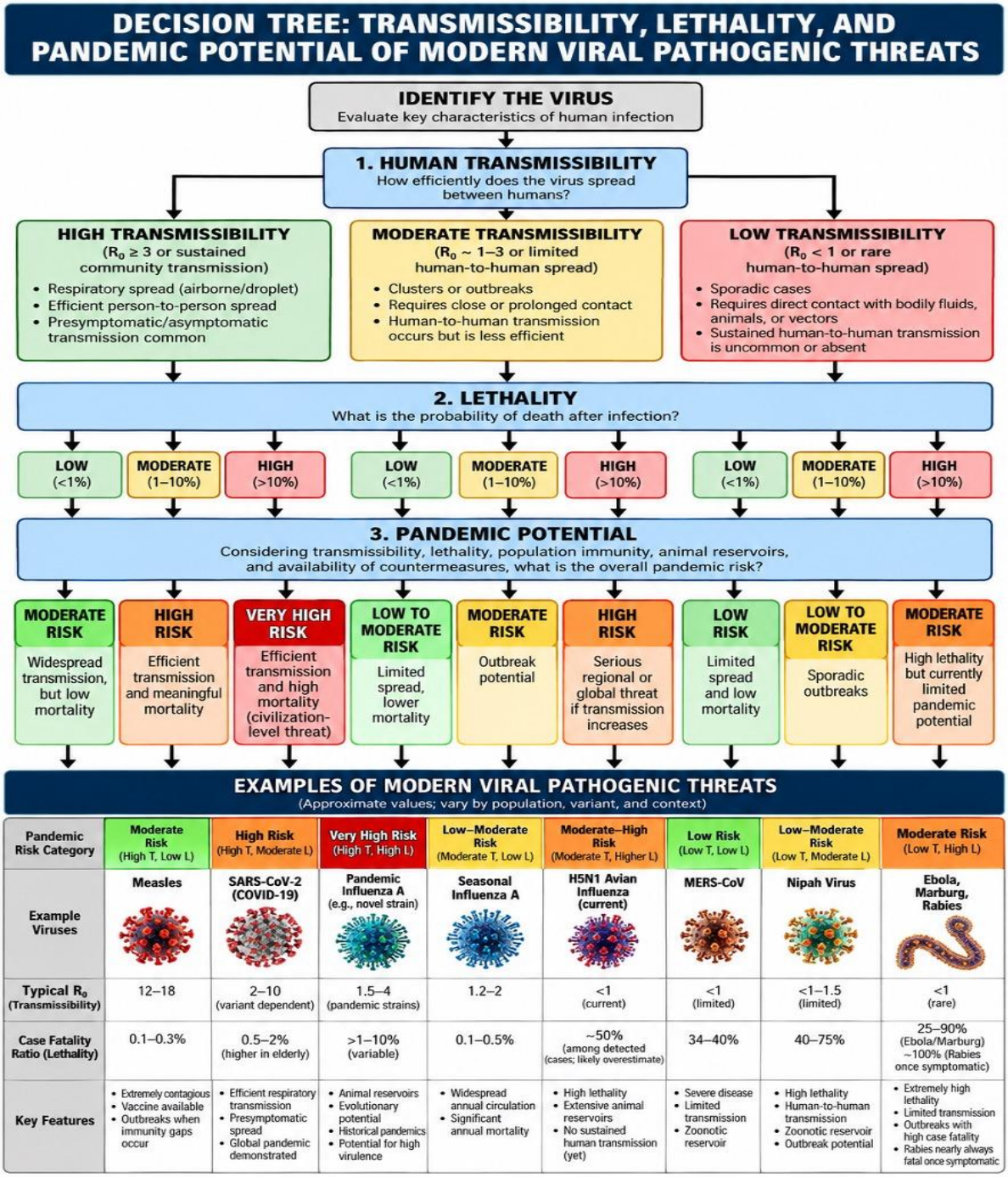


Figure 2

CLINICAL AND EPIDEMIOLOGICAL IMPLICATIONS

Understanding viral threats requires more than memorizing reproduction numbers, case fatality ratios, and pathogen classifications. Medical students must distinguish individual clinical lethality, human-to-human transmissibility, and population-level pandemic potential, recognizing that these characteristics do not necessarily correlate. A virus may cause nearly universal mortality after symptomatic infection yet have negligible epidemic potential, as demonstrated by rabies. Conversely, a highly transmissible respiratory virus with substantially lower infection fatality may produce extensive global mortality, as

demonstrated by SARS-CoV-2. Effective clinical reasoning therefore requires integrating transmission mechanisms, exposure history, host susceptibility, clinical manifestations, diagnostic testing, available countermeasures, and outbreak dynamics.[1,5,6]

From Exposure and Transmission to Pathogen Probability for Causing an Epidemic

The initial assessment should identify the likely route of acquisition and determine whether the patient has relevant epidemiological exposures. Respiratory transmission suggests pathogens such as measles, influenza, or SARS-CoV-2, whereas exposure to infected animals raises concern for rabies, avian influenza, Nipah virus, or other zoonotic infections. Contact with infected bodily fluids, particularly in outbreak settings, should prompt consideration of Ebola or Marburg virus disease. For example, an unvaccinated patient with fever, cough, conjunctivitis, and a generalized maculopapular rash suggests measles; progressive encephalitis following an animal bite raises concern for rabies; and severe febrile illness following exposure to infected livestock, wildlife, or affected healthcare facilities may warrant evaluation for an emerging zoonotic or hemorrhagic fever virus.[10,21,31,36,43] The central principle is that exposure history, transmission route, and clinical syndrome should guide pathogen probability rather than reliance on mortality statistics alone.

From Clinical Presentation to Diagnostic Confirmation

Viral infections frequently produce overlapping manifestations, including fever, respiratory illness, neurological dysfunction, and systemic inflammatory disease. Diagnostic evaluation must therefore integrate clinical findings with epidemiological risk, appropriate specimen collection, and pathogen-specific molecular or antigen-based testing. Respiratory specimens are commonly used for molecular detection of influenza and SARS-CoV-2, whereas suspected measles requires appropriate respiratory testing and serological assessment. Rabies diagnosis may require multiple specimen types, including saliva, nuchal skin biopsy, and serum or cerebrospinal fluid, depending on the clinical circumstances. Suspected Ebola, Marburg, or Nipah virus infection requires specialized laboratory coordination and appropriate infection-control precautions.[10,21,31,36,43] Importantly, clinical severity does not establish transmissibility, and a positive diagnostic result does not independently determine the patient's infectiousness or the likelihood of sustained community spread.

From Pathogen Identification to Clinical Management and Public Health Response

Clinical management depends on the pathogen, disease severity, timing of presentation, host characteristics, and availability of effective countermeasures. Influenza may benefit from early antiviral therapy, whereas severe COVID-19 requires management tailored to disease stage, oxygen requirements, and risk factors. Ebola virus disease caused by ***Zaire ebolavirus*** may be treated with approved monoclonal antibodies, while Nipah and Marburg virus diseases continue to rely primarily on supportive care and investigational countermeasures.[31,38,40]

Prevention is equally pathogen-specific. Measles vaccination interrupts transmission, rabies post-exposure prophylaxis prevents disease before symptom onset, and appropriate

Ebola vaccination can reduce outbreak risk for susceptible individuals. Infection prevention, isolation, contact tracing, and surveillance remain essential, particularly for emerging pathogens with limited therapeutic options.[13,37,46] The essential lesson is that identifying a virus is only the beginning of clinical management; effective care requires anticipating complications, preventing transmission, and selecting interventions appropriate to the pathogen and epidemiological setting.

An Integrated Clinical Decision-Making Framework

For medical students, the evaluation of potentially consequential viral infections can be organized into eight sequential questions:

- **Identify the clinical syndrome:** Is the illness primarily respiratory, neurological, hemorrhagic, systemic, or multisystem?
- **Assess host susceptibility:** What are the patient's age, vaccination status, immune status, comorbidities, and relevant vulnerabilities?
- **Determine the exposure and transmission pathway:** Is acquisition respiratory, zoonotic, vector-borne, or associated with direct contact with infectious bodily fluids?
- **Prioritize likely viral pathogens:** Which viruses best explain the clinical presentation and epidemiological context?
- **Select appropriate diagnostic tests:** Which molecular, antigen-based, serological, or specialized investigations can establish the diagnosis?
- **Initiate appropriate clinical management:** Are pathogen-specific antivirals, immunotherapies, supportive care, or urgent post-exposure interventions indicated?
- **Assess transmission and outbreak-control requirements:** Are isolation, personal protective equipment, contact tracing, vaccination, or public health notification necessary?
- **Reassess clinical and epidemiological risk:** Is the patient deteriorating, are additional exposures occurring, and must management or infection-control measures be modified?

The clinical sequence to memorize: EXPOSURE → HOST → SYNDROME → VIRUS → TEST → TREAT → PREVENT TRANSMISSION → REASSESS

This framework connects bedside clinical reasoning with infectious disease epidemiology and provides a practical foundation for recognizing both severe individual infections and pathogens capable of producing major outbreaks.

CONCLUSION

The world's most consequential viral pathogens differ substantially in their transmissibility, clinical lethality, and capacity to cause widespread disease. No single measure adequately captures the danger posed by a virus. Rather, its overall threat emerges from the interaction

of transmission efficiency, infection severity, population susceptibility, viral evolution, and the availability of effective preventive and therapeutic interventions.

Rabies represents an extreme of clinical lethality, with nearly universal fatality after the onset of symptomatic neurological disease. Nevertheless, its inability to sustain ordinary human-to-human transmission makes pandemic spread exceedingly unlikely.[43,44] Measles represents the opposite epidemiological extreme, exhibiting exceptional contagiousness and the capacity for explosive outbreaks in susceptible populations, despite substantially lower individual lethality and the availability of highly effective vaccination.

Ebola, Marburg, and Nipah viruses exemplify high-consequence emerging pathogens capable of causing devastating disease and exceptionally high case fatality. However, their comparatively constrained human-to-human transmission has thus far limited their capacity for sustained global spread. In contrast, SARS-CoV-2 demonstrated the catastrophic potential of combining efficient respiratory transmission, substantial presymptomatic spread, and clinically significant mortality. Its global impact established that even a pathogen with a relatively modest infection fatality ratio can produce extraordinary population-level mortality when infections become sufficiently widespread.

Among known viral threats, influenza A remains one of the most persistent and biologically plausible sources of a future pandemic. Its extensive animal reservoirs, capacity for mutation and genomic reassortment, established mechanisms of respiratory transmission, and repeated historical pandemic emergence create continuing opportunities for the appearance of antigenically novel human-adapted strains. Seasonal influenza, caused by influenza A and B viruses, already accounts for an estimated 290,000 to 650,000 respiratory deaths annually worldwide.[15] Highly pathogenic avian influenza A(H5N1) introduces an additional concern because historically confirmed human infections have exhibited substantial mortality, although sustained human-to-human transmission has not been established and preferential detection of severe cases likely inflates the observed case fatality ratio.

The greatest future danger therefore lies not necessarily with the most contagious or most lethal virus, but with a pathogen capable of sustaining extensive human transmission while causing substantial morbidity and mortality across large, susceptible populations. Particularly concerning would be an emerging respiratory virus combining efficient presymptomatic transmission, limited preexisting immunity, clinically important virulence, evolutionary adaptability, and opportunities for recurrent zoonotic introduction. These characteristics need not occur at their theoretical extremes to produce a global health catastrophe.

The central lesson of COVID-19 is that extreme individual lethality is not required for catastrophic population-level mortality. Conversely, Ebola, Marburg, Nipah, and H5N1 demonstrate that viruses with substantially greater observed case fatality already exist in nature, even though their current transmission characteristics have constrained their pandemic potential. The possibility that an emerging virus could combine influenza-like transmission efficiency with substantially greater clinical virulence remains among the most consequential biological threats to global health.

Nevertheless, pandemic preparedness must extend beyond the pathogens already recognized as dangerous. The World Health Organization's expanded prioritization framework, encompassing entire viral families and the concept of Disease X, acknowledges

that the next major threat may emerge from a known virus, an overlooked member of an established viral family, or a previously unidentified human pathogen.

Ultimately, the most effective defense against future viral pandemics is not the ability to predict a single pathogen, but the capacity to recognize emerging threats early, characterize their transmission and severity rapidly, and deploy effective countermeasures before localized outbreaks become global crises. Sustained zoonotic and genomic surveillance, adaptable vaccine and therapeutic platforms, resilient healthcare systems, and coordinated international public health responses are therefore essential to reducing the consequences of both known and unforeseen viral threats.

Disclosure: The authors did not report any disclosures.

REFERENCES

1. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A. 2004;101(16):6146-6151. doi:10.1073/pnas.0307506101
2. Anderson RM, Heesterbeek H, Klinkenberg D, Hollingsworth TD. How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet. 2020;395(10228):931-934. doi:10.1016/S0140-6736(20)30567-5
3. World Health Organization. Prioritizing diseases for research and development in emergency contexts. Accessed October 14, 2026. https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts
4. World Health Organization. Pathogens Prioritization: A Scientific Framework for Epidemic and Pandemic Research Preparedness. World Health Organization; 2024. Published July 30, 2024. WHO report
5. Delamater PL, Street EJ, Leslie TF, Yang YT, Jacobsen KH. Complexity of the basic reproduction number (R_0). Emerg Infect Dis. 2019;25(1):1-4. doi:10.3201/eid2501.171901
6. Lipsitch M, Donnelly CA, Fraser C, et al. Potential biases in estimating absolute and relative case-fatality risks during outbreaks. PLoS Negl Trop Dis. 2015;9(7):e0003846. doi:10.1371/journal.pntd.0003846
7. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. Int J Infect Dis. 2020;101:138-148. doi:10.1016/j.ijid.2020.09.1464
8. World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2024. World Health Organization; 2024. WHO influenza surveillance.
9. Guerra FM, Bolotin S, Lim G, et al. The basic reproduction number (R_0) of measles: a systematic review. Lancet Infect Dis. 2017;17(12):e420-e428. doi:10.1016/S1473-3099(17)30307-9
10. Centers for Disease Control and Prevention. Clinical overview of measles. Updated July 15, 2024. https://www.cdc.gov/measles/hcp/clinical-overview/index.html
11. Moss WJ. Measles. Lancet. 2017;390(10111):2490-2502. doi:10.1016/S0140-6736(17)31463-0
12. Mina MJ, Metcalf CJE, de Swart RL, Osterhaus ADME, Grenfell BT. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. Science. 2015;348(6235):694-699. doi:10.1126/science.aaa3662

13. World Health Organization. Measles vaccines: WHO position paper, April 2017. Wkly Epidemiol Rec. 2017;92(17):205-227. WHO publication

14. Patel MK, Goodson JL, Alexander JP Jr, et al. Progress toward regional measles elimination, worldwide, 2000-2019. MMWR Morb Mortal Wkly Rep. 2020;69(45):1700-1705. doi:10.15585/mmwr.mm6945a6

15. World Health Organization. Influenza (seasonal). Updated February 28, 2025. Accessed October 14, 2026. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)

16. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev. 1992;56(1):152-179. doi:10.1128/mr.56.1.152-179.1992

17. Taubenberger JK, Morens DM. The 1918 influenza pandemic and its legacy. Cold Spring Harb Perspect Med. 2020;10(10):a038695. doi:10.1101/cshperspect.a038695

18. Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. Emerg Infect Dis. 2006;12(1):15-22. doi:10.3201/eid1201.050979

19. Salmanton-García J, et al. Predicting the next pandemic: VACCELERATE ranking of the World Health Organization's Blueprint for Action to Prevent Epidemics. Travel Med Infect Dis. 2024;57:102676. doi:10.1016/j.tmaid.2023.102676

20. Centers for Disease Control and Prevention. Risk to people in the United States from highly pathogenic avian influenza A(H5N1) viruses. Published February 28, 2025. https://www.cdc.gov/cfa-qualitative-assessments/php/data-research/h5-risk-assessment.html.

21. Centers for Disease Control and Prevention. Highly pathogenic avian influenza A(H5N1) virus: interim recommendations for prevention, monitoring, and public health investigations. https://www.cdc.gov/bird-flu/prevention/hpai-interim-recommendations.html.

22. Herfst S, Schrauwen EJA, Linster M, et al. Airborne transmission of influenza A/H5N1 virus between ferrets. Science. 2012;336(6088):1534-1541. doi:10.1126/science.1213362

23. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-675. doi:10.1038/s41591-020-0869-5

24. Johansson MA, Quandelacy TM, Kada S, et al. SARS-CoV-2 transmission from people without COVID-19 symptoms. JAMA Netw Open. 2021;4(1):e2035057. doi:10.1001/jamanetworkopen.2020.35057

25. World Health Organization. Global excess deaths associated with COVID-19, January 2020-December 2021. Published May 5, 2022. https://www.who.int/news/item/05-05-2022-14.9-million-excess-deaths-were-associated-with-the-covid-19-pandemic-in-2020-and-2021

26. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol. 2021;19(7):409-424. doi:10.1038/s41579-021-00573-0

27. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). Published August 4, 2022. https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)

28. Azhar EI, El-Kafrawy SA, Farraj SA, et al. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med. 2014;370(26):2499-2505. doi:10.1056/NEJMoa1401505

29. Cauchemez S, Fraser C, Van Kerkhove MD, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. Lancet Infect Dis. 2014;14(1):50-56. doi:10.1016/S1473-3099(13)70304-9

30. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17(3):181-192. doi:10.1038/s41579-018-0118-9

31. World Health Organization. Nipah virus. Published May 30, 2018. https://www.who.int/news-room/fact-sheets/detail/nipah-virus

32. Ang BSP, Lim TCC, Wang L. Nipah virus infection. J Clin Microbiol. 2018;56(6):e01875-17. doi:10.1128/JCM.01875-17

33. Luby SP, Gurley ES, Hossain MJ. Transmission of human infection with Nipah virus. Clin Infect Dis. 2009;49(11):1743-1748. doi:10.1086/647951

34. Nikolay B, Salje H, Hossain MJ, et al. Transmission of Nipah virus: 14 years of investigations in Bangladesh. N Engl J Med. 2019;380(19):1804-1814. doi:10.1056/NEJMoa1805376

35. Satterfield BA, Dawes BE, Milligan GN. Status of vaccine research and development of vaccines for Nipah virus. Vaccine. 2016;34(26):2971-2975. doi:10.1016/j.vaccine.2015.12.075

36. World Health Organization. Ebola disease. https://www.who.int/news-room/fact-sheets/detail/ebola-disease

37. Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet. 2017;389(10068):505-518. doi:10.1016/S0140-6736(16)32621-6

38. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293-2303. doi:10.1056/NEJMoa1910993

39. Centers for Disease Control and Prevention. 2014-2016 Ebola outbreak in West Africa. https://www.cdc.gov/ebola/outbreaks/2014-west-africa/index.html

40. World Health Organization. Marburg virus disease. https://www.who.int/news-room/fact-sheets/detail/marburg-virus-disease

41. Towner JS, Amman BR, Sealy TK, et al. Isolation of genetically diverse Marburg viruses from Egyptian fruit bats. PLoS Pathog. 2009;5(7):e1000536. doi:10.1371/journal.ppat.1000536

42. Kortepeter MG, Dierberg K, Shenoy ES, Cieslak TJ. Marburg virus disease: a summary for clinicians. Int J Infect Dis. 2020;99:233-242. doi:10.1016/j.ijid.2020.07.042

43. Centers for Disease Control and Prevention. Rabies: infection control in healthcare personnel. https://www.cdc.gov/infection-control/hcp/healthcare-personnel-epidemiology-control/rabies.html

44. Fooks AR, Banyard AC, Horton DL, Johnson N, McElhinney LM, Jackson AC. Current status of rabies and prospects for elimination. Lancet. 2014;384(9951):1389-1399. doi:10.1016/S0140-6736(13)62707-5

45. Hampson K, Coudeville L, Lembo T, et al. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis. 2015;9(4):e0003709. doi:10.1371/journal.pntd.0003709

46. Centers for Disease Control and Prevention. Rabies. https://www.cdc.gov/rabies/about/index.html

47. World Health Organization. Smallpox. https://www.who.int/health-topics/smallpox

48. Fenner F, Henderson DA, Arita I, Ježek Z, Ladnyi ID. Smallpox and Its Eradication. World Health Organization; 1988. https://iris.who.int/handle/10665/39485

49. World Health Organization. Smallpox: questions and answers. https://www.who.int/news-room/questions-and-answers/item/smallpox