# Pandemic origins and a One Health approach to preparedness and prevention: Solutions based on SARS-CoV-2 and other RNA viruses

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COVID-19 is the latest zoonotic RNA virus epidemic of concern. Learning how it began and spread will help to determine how to reduce the risk of future events. We review major RNA virus outbreaks since 1967 to identify common features and opportunities to prevent emergence, including ancestral viral origins in birds, bats, and other mammals; animal reservoirs and intermediate hosts; and pathways for zoonotic spillover and community spread, leading to local, regional, or international outbreaks. The increasing scientific evidence concerning the origins of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is most consistent with a zoonotic origin and a spillover pathway from wildlife to people via wildlife farming and the wildlife trade. We apply what we know about these outbreaks to identify relevant, feasible, and implementable interventions. We identify three primary targets for pandemic prevention and preparedness: first, smart surveillance coupled with epidemiological risk assessment across wildlife–livestock–human (One Health) spillover interfaces; second, research to enhance pandemic preparedness and expedite development of vaccines and therapeutics; and third, strategies to reduce underlying drivers of spillover risk and spread and reduce the influence of misinformation. For all three, continued efforts to improve and integrate biosafety and biosecurity with the implementation of a One Health approach are essential. We discuss new models to address the challenges of creating an inclusive and effective governance structure, with the necessary stable funding for cross-disciplinary collaborative research. Finally, we offer recommendations for feasible actions to close the knowledge gaps across the One Health continuum and improve preparedness and response in the future.

pandemic preparedness j COVID-19 origins and spread j Drivers of emerging infectious diseases j spillover and spillback j One Health solutions

Over the past century, emerging infectious diseases (EIDs) have caused numerous outbreaks, severe illnesses, and many deaths (1). Most had zoonotic (animal to human) origins, and some reached pandemic proportions. The most problematic EIDs were caused by RNA viruses, from influenza A virus pandemics in 1918, 1957, 1968, and 2009 to HIV first recognized in 1981 and now Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the cause of COVID-19. Their continuing emergence highlights a recurrent lesson; the world has largely failed to meet the challenge to be better prepared to prevent or respond to the next outbreak, whatever the etiology. The increased frequency of new EIDs is driven by many factors from microbial evolution to human and domestic animal population growth; land use and climate change; expanding human–animal–environment interfaces; and human behavior, travel, and trade (2, 3). These varied factors are best addressed with a comprehensive One Health approach, recently defined as "an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems" (4). One Health engages diverse disciplines and all levels of society to collaborate; promote human, animal, and ecosystem health; and respond to health and environmental threats. Translating

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Competing interest statement: Several authors have historic and/or current research collaborations with multiple countries in the course of their work on emerging infections, and for some, this includes Chinese institutions researching bat-associated coronaviruses.

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this into action across borders, cultures, and economic models has been too slow and limited to be effective.

We are international scientists with diverse disciplinary expertise in human, animal, and public health; virology; epidemiology; wildlife biology; ecology; and EIDs organized in 2020 as a task force of the Lancet COVID-19 Commission. Since late 2021, we convened as an Independent Task Force on COVID-19 and Other Pandemic Origins, Prevention and Response. We reviewed recent scientific publications, interviewed scientists with diverse expertise and experience (*SI Appendix*, Table S1), and gained insight from our own experience to better understand what drives pandemic emergence, learn from prior zoonotic RNA virus spillovers, and identify gaps to address. This report presents our conclusions and recommendations for an action agenda.

## An Increasing Pandemic Threat Driven by Human Activity

COVID-19 is the latest human pandemic caused by an RNA virus (5). In the past half century, there have been multiple RNA virus epidemics or pandemics (influenza 1957, 1968, and 2009; HIV; SARS-CoV; Middle East Respiratory Syndrome (MERS)-CoV; Zika; SARS-CoV-2; and others), thousands of recognized outbreaks, and the emergence of previously unknown pathogens (Fig. 1 and *SI Appendix*, Tables S2 and S3) (2, 6). Understanding how these outbreaks originate can guide how to prevent, mitigate, or respond to future EIDs, including non-RNA virus pathogens (7). Analyzing underlying drivers of EIDs indicates where future pathogens are likely to emerge and focuses resource allocation for prevention or control (6). EID hot spots are predominantly in countries with rich biodiversity, dense and growing human populations, rapidly developing economies dependent on transformative land use, and expanding livestock and crop production (8). Climate change already affects disease emergence and is projected to drive increasing future viral spillovers (9). The wildlife trade has grown significantly in complexity and scale, expanding threats to human and animal health (10, 11). Traditional wildlife hunting to provide food for small rural communities, particularly in Southeast Asia and southern China, has been transformed into an industrial-scale process that employed around 14 million people in China alone in 2016 (12). Wildlife trade supply chains now include thousands of wildlife farms with mixed captive-bred and wild-caught animals transporting live animals, carcasses, or products regionally and nationally, while the international trade in live animals and their products has continued to expand (11). Zoonotic spillovers, whether from wildlife, livestock, or domestic animals, are an urgent communicable disease threat, even though many are unable to spread efficiently among people (e.g., MERS-CoV) or lack the human-to-human connectivity essential for community spread (e.g., Ebola virus in isolated rural communities) (*SI Appendix*, Table S2) (1). RNA viruses, constituting up to 44% of all EIDs, are adept at circumventing these barriers due to short generation times, error-prone replication cycles, and faster evolutionary rates that may increase capacity for successful spillover from animals to humans and subsequent spread (6, 13–16).

In this report, we review past RNA virus outbreaks; examine the origins, evolution, and lessons from COVID-19; and identify approaches to reduce threats and consequences of future outbreaks.

## What Has Been Learned (and Relearned) from Previous RNA Virus Outbreaks

Influenza type A illustrates lessons pertinent for many other emergent RNA viruses (Box 1 and *SI Appendix*, Tables S2 and S3). Influenza A virus infects multiple host species, such as birds, swine, aquatic mammals, bats, and humans. Interspecies transmission, usually associated with reassortment of the segmented influenza genome, leads to periodic pandemics in people or epizootics in animals. For example, the 1997 Hong Kong outbreak of highly pathogenic avian influenza (HPAI) A H5N1 was traced to infected poultry in live markets, triggering a cull of all poultry in Hong Kong markets and farms and control of the outbreak virus. However, active surveillance of imported poultry demonstrated that precursor viruses remained in circulation elsewhere. By 2004, 10 countries in Asia reported outbreaks of HPAI in poultry, with zoonotic spillover in 4 countries. By 2005, the virus reached the Middle East, Africa, and Europe via migratory wild birds and the poultry trade (17). While some countries recognized its introduction and intervened to control

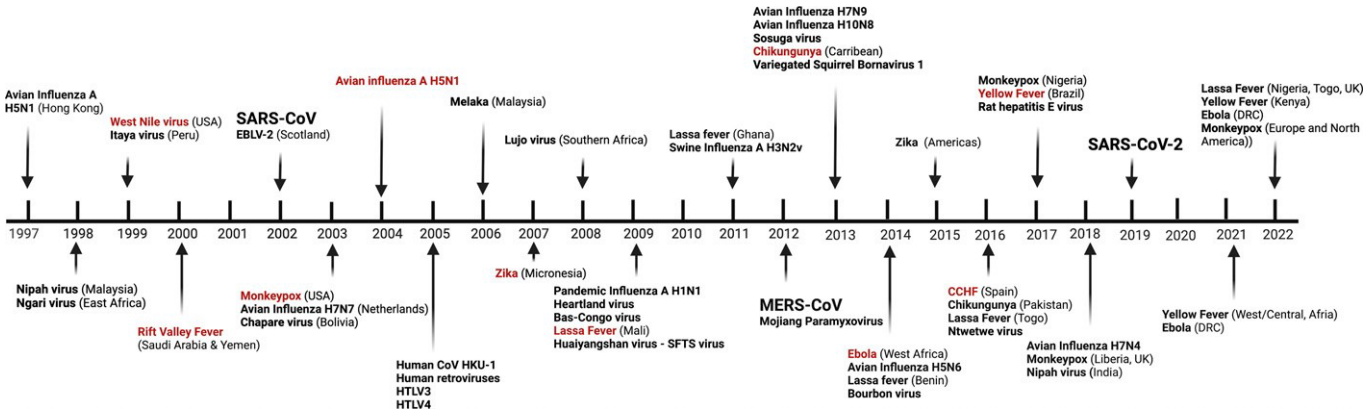


Fig. 1. Time line of the emergence and repeat spillovers to humans for a sample of RNA viruses and Monkeypox virus from 1997 to present. Repeat spillovers are indicated in red (the countries involved are in parentheses). The large font identifies the three recent emerging epidemic/pandemic CoVs. EBLV-2, European Bat Lyssavirus Type 2; DRC, Democratic Republic of Congo; HKU-1, HKU-1 coronavirus; HTLV3, Human T-lymphotropic virus Type 3; HTLV4, Human T-lymphotropic virus Type 4; SFTS, Severe Fever with Thrombocytopenia Syndrome virus; CCHF, Crimean-Congo Hemorrhagic Fever virus.

Box 1. Findings from 10 emerging RNA virus outbreaks in humans, 1967 to 2015 (*SI Appendix*, Table S2).

- All etiologic agents evolved from ancestral animal viruses.
- All were zoonotically transmitted to humans.
- It can take decades to identify the spillover pathway to humans.
- Repeated spillovers are common.
- All but two were readily transmissible from human to human.

spread, it remained enzootic where surveillance was weak, delaying timely interventions. HPAI reassortants (H5N6, H5N8) appeared worldwide, with >500 million birds in more than 80 countries killed by disease or culled for control and over 900 cases of human disease with 490 deaths (18). In contrast, no locally acquired zoonotic avian influenza A virus spillovers occurred in Hong Kong after 1997, attributable to active surveillance and evidence-based interventions implemented in a One Health context (19).

The 2009 influenza A pandemic was due to an H1N1 virus resulting from sequential reassortment of swine, human, and avian influenza A viruses. Its H1 hemagglutinin was derived from the 1918 influenza A virus, which remained the classical swine influenza virus for decades. It took 7 y to identify its immediate ancestor. Emergence was facilitated by the global trade in domestic livestock and the introduction of a precursor virus, Eurasian avian-like swine influenza virus, to North America. As the 2009 human pandemic virus spread globally, it spilled back into swine around the world, genetically reassorting with existing swine influenza A viruses, enhancing the diversity of swine influenza A viruses worldwide, and increasing future influenza A pandemic potential. The time line of emergence and repeat spillovers for influenza A, other RNA viruses, and Monkeypox virus over the past 25 y reveals that both emergence and repeat spillovers are extremely common (Fig. 1).

## Coronaviruses Are a High Pandemic Risk

The emergence of three coronaviruses (CoVs) causing highly consequential human outbreaks in the past two decades points to the importance of this virus family as a future pandemic threat. The history of CoVs is enlightening. First discovered in 1931 during investigation of a fatal respiratory disease of poultry (20), CoVs are a large diverse family circulating in wildlife, with more than 4,800 sequences reported thus far (21). They are divided into four genera: alpha- and beta-CoVs with a broad mammalian host range extending to humans and gamma- and delta-CoVs, predominantly in avian species, a few mammals, and rarely, in humans (*SI Appendix*, Fig. S1). Presently, there are just seven known human CoVs, including four common cold viruses that occasionally cause pneumonia in high-risk hosts and three that cause severe acute respiratory syndromes (SARS, MERS, and COVID-19) (Box 2 and *SI Appendix*, Table S3).

Box 2. Common features of human CoVs.

- Ancestral hosts for human CoVs were bats, other mammals, or avian species.
- All were originally zoonotically transmitted to humans.
- Common cold viruses are now endemic in humans.
- Intermediate hosts are known for two of the three CoVs causing severe acute respiratory syndromes.
- Human-to-human transmission ranges from poor to highly efficient.

Molecular clock analyses of common cold CoVs indicate that the original zoonotic spillovers occurred at least 100 to 1,000 y ago (Fig. 2). Common cold CoVs have since become endemic in humans, transmitted via respiratory droplets, aerosols, or fomites. The remarkable emergence of three highly consequential new CoVs (SARS-CoV, MERS-CoV, and SARS-CoV-2) in humans in the past two decades likely reflects increased spillover risks via land use change; greater contact between humans, livestock, and wildlife; and expanding wildlife farming, trade, live food markets, and global travel and trade.

The ancestral hosts of the SARS-CoV and SARS-CoV-2 viral lineages are thought to be *Rhinolophus* (rhinolophid) spp. bats (22) and *Pipistrellus* and *Neoromicia* (vespertilionid) bats for MERS-CoV (23) (*SI Appendix*, Fig. S1). Evidence indicates SARS-CoV and MERS-CoV emerged indirectly from bats via an intermediate animal host subsequently transmitting infection to people. For SARS-CoV, it most likely involved infected masked palm civets (*Paguma larvata*) or possibly common raccoon dogs (*Nyctereutes procyonoides*) or Chinese ferret badgers (*Melogale moschata*) in live animal markets (*SI Appendix*, Table S3). There were four individual zoonotic infections in China a few months after the initial SARS-CoV outbreak, but no subsequent zoonotic spillovers were identified (24); however, there is no basis to presume SARS-CoV has become extinct. Closely related CoVs expressing spike (S) proteins binding to angiotensin-converting enzyme (ACE2), the human receptor protein, have been identified in bats, raising the possibility that a virus closely related to SARS-CoV could reemerge (22, 25). MERS-CoV was circulating endemically in dromedary camels (*Camelus dromedarius*) for decades before human cases appeared. It remains endemic in these animals, resulting in continuing zoonotic spillovers (26).

## Animal CoVs Provide Important One Health Lessons for Human CoV Evolution and Disease

Animal CoVs are a substantial risk to farmed animals and people because of their ability to mutate, recombine, and become more transmissible and/or virulent and their history of cross-species and zoonotic transmission (27). They provide a One Health perspective in nature to help us better understand CoV evolutionary trajectories and the risk of human spillovers (Box 3).

For example, mutations, deletions, and recombination events have created multiple lineages of porcine CoVs with altered virulence, tissue tropism, and potential for cross-species infections (Box 3, Fig. 2, and *SI Appendix*, Table S4) (11). These include transmissible gastroenteritis virus (TGEV), described in 1946; porcine epidemic diarrhea virus (PEDV), which emerged in Europe in the 1970s, recently reappeared as a highly virulent variant in China and the United States, and now is endemic worldwide; recombinants that include elements of both; and porcine respiratory coronavirus (PRCV), a TGEV deletion variant with respiratory tract tropism

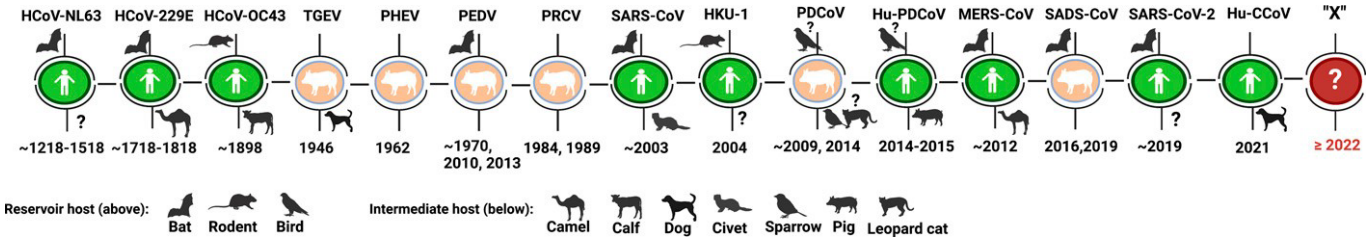


Fig. 2. Time line of the emergence of CoVs in people or livestock over the past millennium. Evidence supports the origin and emergence of many of these viruses in wildlife, including bats, other mammals, and avian species, often involving an intermediate animal host. The time of the initial spillover as determined by molecular clock analysis or the discovery of the virus by epidemiologic or virologic methods, presumed reservoir host, and the major intermediate hosts for human and swine CoVs are depicted. Black animal silhouettes indicate the likely reservoir (above) or intermediate host (below). PDCoV, porcine delta-coronavirus; SADS-CoV, swine acute diarrhea syndrome coronavirus. HCoV, Human coronavirus; PHEV, Porcine Hemagglutinating Encephalomyelitis virus; HKU-1, HKU-1 coronavirus; Hu-PDCoV, Human-Porcine Delta coronavirus; Hu-CCoV, Human-Canine coronavirus.

that transmits via aerosols (28). Avian-origin porcine delta-CoV has recently been recovered from humans with febrile illnesses (29), raising concerns that it could mirror recombination events for influenza viruses and potentially become a future World Health Organization (WHO) pandemic disease "X" (30). The bat-origin swine acute diarrhea syndrome CoV emerged in pigs in 2016 (31) and also replicates in primary human airway epithelial cells, suggesting it too has future spillover potential to humans (32).

The increasing global population of farmed and domestic animals provides other cross-species transmission opportunities. Canine CCoV, feline coronavirus (FCoV), and TGEV are a single CoV species within a multihost reservoir community in dogs, cats, and pigs (33), with rare spillovers to humans (Hu-CCoV) *(SI Appendix*, Table S3). Beta-CoVs circulating in cattle and wild cervids occasionally infect birds or humans (34–36). Recent spillover of SARS-CoV-2 from humans to white-tailed deer may represent another long-term reservoir community with spillback potential to humans (*SI Appendix*, Table S4) (37, 38). Spillover of SARS-CoV-2 from humans to farmed mink and mink-to-human spillback are already well described (39). Evolution of these viruses in susceptible animal hosts represents a plausible threat for future disease outbreaks among animals and humans.

## The SARS-CoV-2 (COVID-19) Pandemic

Analyzing the origin, early spread, and pandemic emergence of SARS-CoV-2 is critical to understand how to prevent and control future zoonotic viral emergence. The initial phase of COVID-19, from December 2019 through January 2020 in Wuhan, China, began with the recognition of a cluster of patients with SARS-like illnesses. By early January 2020, a novel Severe Acute Respiratory Syndrome-related coronavirus (SARSr-CoV; subsequently renamed SARS-CoV-2) was identified by next-generation sequencing (NGS) of human respiratory samples. This quickly led to a PCR diagnostic to track virus spread within and outside of China (*SI Appendix*, Fig. S2) and evidence of human-to-human transmission within families. On 30 January 2020, WHO declared the outbreak a Public Health Emergency of International Concern.

The prevaccine phase 2, from February to the end of 2020, was an unnecessary tragedy as national leaders in many countries denied the seriousness of the outbreak, failed to provide reliable information to the public, or failed to promote the use of effective public health measures (40). Early warnings without follow-up actions have limited impact. By the end of 2020, over 100 million cases and 2 million deaths had occurred, and many countries were struggling to sustain patient care and public health capacity. The major triumph was the development and emergency use approval of vaccines. However, production was insufficient for global needs, further compromised when some high-income countries made advance purchase agreements for most of the supply. This practice, characterized as "vaccine nationalism," precluded equitable vaccine sharing based on a strategic plan to control pandemic spread and impact at the global level. Monoclonal antibodies and antivirals were also approved, but infusion capacity limited utilization of antibodies while therapeutics became available in just a few countries.

The vaccine and emerging variants phase 3 has continued from January 2021 to the present. While several vaccines have been safe and highly effective in reducing severe illness and death, even in high-risk individuals, in some countries many people with access to these vaccines have hesitated or simply refused to be immunized. Continuing transmission of infection increases the likelihood of emerging variants, an expected consequence of mutations accumulating when an RNA virus outbreak is not contained. By the end of 2021, WHO had designated five strains as variants of concern because their attributes suggested potential enhanced transmission, virulence, or immune evasion. Two, Delta and Omicron, surged sequentially in mid- to late 2021, each displacing the prior circulating variant and increasing infections, hospitalizations, and deaths. The future is uncertain as more transmissible Omicron variants emerge and spread globally. By 1 August 2022, WHO reported well over half a billion cases and more than 6.4 million deaths

**Box 3. One Heath implications from evolving swine CoVs.**

- Variants can arise with altered tissue tropism and virulence.
- New viruses can emerge from bat ancestral hosts to cause global (e.g., PEDV) or regional epidemics (e.g., Swine Acute Diarrhea Syndrome virus [SADS]).
- Established viruses can disappear and then, re-emerge in other regions with increased virulence and lethality (e.g., PEDV).
- Recombinants of newly emerged and endemic strains can escape immunity (TGEV/PEDV) or have reduced virulence (TGEV/PRCV).
- Mutant animal CoV strains can spillover to humans (Human-Porcine Delta Coronavirus [Hu-PDCoV]) or remain zoonotic threats (SADS).

worldwide. The real toll of SARS-CoV-2–related deaths is considerably greater, with at least 14.91 million excess deaths reported by 31 December 2021 or 9.49 million more than previously attributed to SARS-CoV-2 (https://www.who.int/data/stories/global-excess-deaths-associated-with-covid-19-january-2020-december-2021).

A recent analysis of 10 community-based longitudinal studies of patients in the United Kingdom with a diagnosis of COVID-19 in their electronic health care records identified 7.8 to 17% with symptoms persisting beyond 12 wk, termed "long COVID" (long coronavirus disease) (41). This represents an additional long-term health and economic burden of the pandemic. Unfortunately, systematic clinical research of long COVID has just begun, the underlying pathophysiology is not understood, and there are no clearly effective interventions. We may also be at the cusp of another epidemiological phase of COVID-19, with continued community circulation, evolution of the virus, and increasing endemicity in humans and animals (39, 42).

The Origins of SARS-CoV-2 and How the Outbreak Began. Understanding the origins of novel diseases is necessary to improve preparedness for future EIDs and often requires years of research to accumulate convincing evidence (Figs. 1 and 2 and *SI Appendix*, Tables S2 and S3). EIDs caused by novel zoonotic viral agents are usually discovered sometime after the initial zoonotic transmission when a cluster of human cases is recognized. This delay diminishes the ability to prevent further dissemination or to collect and preserve early samples important to identify the pathway involved. Most EIDs are zoonotic, and most of these have wildlife origins (6); however, identifying the ancestral reservoir or intermediary host species usually requires substantial field and laboratory research involving multiple disciplines. This can conflict with outbreak control priorities, further delaying the process.

The first new CoV outbreak of the twenty-first century, SARS, emerged in 2003 within live wildlife markets of Guangdong, spilling over from bats to intermediate amplifier hosts (civets, possibly raccoon dogs or another susceptible species) to people working in wildlife markets and restaurants, followed by international spread via infected travelers. The closest relatives of SARS-CoV were found in *Rhinolophus* spp. bats in Yunnan province (22). Spillover, amplification, and spread could have occurred at any point during capture of wildlife, farming of intermediate hosts, and transport or trade of live animals across the vast network of farms and markets. The pathway of emergence of SARS-CoV-2 is still under scrutiny; however, substantial research published before and after the virus emerged indicates that it too likely evolved from ancestral bat CoVs. Several CoVs with high overall percentage sequence homology with SARS-CoV-2, even greater homology with the S protein, and the use of ACE2 as the cell receptor have been found in China and Southeast Asia (*SI Appendix*, Table S5). They do not express a functional furin cleavage site (FCS), which facilitates cell entry of SARS-CoV-2. However, other CoVs possess FCS-like motifs, suggesting that this cleavage strategy may coevolve with the host: for example, MERS-CoV or a rat alpha-CoV with an FCS nearly identical to SARS-CoV-2 identified at wildlife farms, train stations, and hotels in southern China (43). Efforts to determine if SARS-CoV-2–related viruses may evolve an FCS have not demonstrated its occurrence using humanized mouse or primate animal models; however, these hosts are not associated with any hypothesized pathway of emergence via the wildlife trade (*SI Appendix*, Table S6). The failure to detect the evolution of an FCS in closely related viruses from Laos after repeated passage in human cells in vitro suggests that it was unlikely to have evolved into SARS-CoV-2 during laboratory passage in cell culture (*SI Appendix*, Table S6).

Substantial evidence has amassed over the last 2 1/2 y suggesting that COVID-19 originated via a similar pathway to SARS involving a spillover from bats to intermediate hosts in wildlife farms or markets, and then to people within the wildlife trade, leading to the first known cluster in the Huanan Seafood Market (HSM) in Wuhan in December 2019 (*SI Appendix*, Table S6). Evidence includes analysis of SARSr-CoV and SARS-CoV-2 genomes, spatial and epidemiological data of the early cases, live animal market sales in Wuhan, and characterization of related wildlife CoVs. Epidemiological analyses show that COVID-19 cases identified in December 2019 lived closer to HSM than expected by chance, whether or not they were epidemiologically linked to the market (44). The index patient in the community, who worked at HSM, developed symptoms on 10 December 2019, indicating that initial human community transmission likely began weeks before. Live mammalian species known to be susceptible to or harbor SARSr-CoVs (raccoon dogs, ferret badgers, others) were regularly sold at HSM just prior to the first known human cases, including animals farmed in southern China where close relatives of SARS-CoV-2 are present in bats (45, 46). Raccoon dogs, extensively bred for food and fur, are susceptible to infection but not illness and can transmit the virus via aerosols to naïve animals in close proximity (47). Of 893 environmental samples within HSM, nearby HSM warehouses, and sewage wells collected on or after 1 January 2020, 72 (8%) were PCR positive, and live virus was recovered from 3 of 27 samples tested (48). The inability to identify SARS-CoV-2 in retrospective surveys of >80,000 animals in China does not refute the presence of an intermediary host because samples were mostly domestic livestock or zoo animals, were often historic samples too small in per-species sample size to rule out infection, or were collected where no close relatives of SARS-CoV-2 have been identified in bats (46).

Nearly all positive environmental samples evaluated (31 of 33) at HSM tracked to the section where live animal stalls were located. Five, including from cages and other objects related to holding live animals in the market, came from a stall known to be selling live animals in late 2019. Phylogenetic analysis of the A and B lineages of SARS-CoV-2 circulating in Wuhan in December 2019 suggests these represent at least two cross-species virus transmission events, indicative of continual exposure to a diverse source consistent with transmission from an intermediate host animal to humans in a live animal market (49).

Some early alternative hypotheses for the emergence of SARS-CoV-2 postulated that it was constructed, cultured, or experimentally manipulated in a laboratory or was associated with field surveillance of bats, leading to an intentional or accidental release. The suggestion that SARS-CoV-2 was created in a laboratory is now widely considered less

probable than emergence via wildlife farms and the wildlife trade, including by the US intelligence community (https://www.dni.gov/files/ODNI/documents/assessments/Unclassified-Summary-of-Assessment-on-COVID-19-Origins.pdf). However, laboratory accidents do happen, and no independent formal audit of the Wuhan laboratory facilities has been possible in the wake of geopolitical conflicts. To assess the relative weight of evidence for these different hypotheses, we reviewed the literature and assessed the rigor of the publications and their sources (*SI Appendix*, Table S6). Considerable scientific peer-reviewed evidence supports COVID-19's origin as a zoonotic infection within the wildlife trade (*SI Appendix*, Table S6), as in many prior outbreaks (Boxes 1 and 2 and *SI Appendix*, Tables S2 and S3). While a laboratory leak cannot be ruled out, no verifiable evidence or scientific data are available to support this interpretation. The importance of critically evaluating evidence indicating a zoonotic link to wildlife is that it leads to implementable One Health–oriented changes in practice that can reduce the likelihood of another similar future occurrence. Importantly, this presents no conflict with continuous efforts to improve laboratory and field biosafety and biosecurity.

Messaging and Misinformation about SARS-CoV-2. The trajectory for any new EID from an outbreak to an epidemic or pandemic depends in part on human behaviors that condition spread. Community transmission of respiratory EIDs, including SARS-CoV-2, can be reduced by diagnostic testing, contact tracing, and isolation of confirmed cases and individuals with known or suspected exposure. Proper use of effective masks, social distancing, avoidance of crowded indoor gatherings, and immunization are all effective, simple, voluntary preventive behaviors. Consistent effective messaging is essential to encourage people to accept inconveniences and change behavior. Mandating public health measures can also be effective but often generates local or generalized resistance by portions of the population. While misinformation is not a new phenomenon, it is remarkable how much has been disseminated about COVID-19 by some media sources; dramatically amplified via social media; and intensified by distrust of scientific, public health, or government experts (50). Expanded research on misinformation and its impact on belief systems is of the highest priority to guide interventions. Compounding these concerns, messaging of evidence-based information or current best practice by health professionals has often been inconsistent, encouraging some to deny the risks and continue risky behaviors. Pandemic control will require more effective strategies to counter these influences.

## Looking Forward: Implementing Three Fundamental Approaches

COVID-19 is the latest in a continuing series of RNA virus outbreaks (Fig. 1); however, its health, social, behavioral, economic, and political consequences have been enormous. These impacts are precisely why we must learn from the ongoing pandemic, look forward, and identify things we can change to reduce the risk of future pandemics, prevent them when possible, or rapidly mitigate and control them when necessary.

There are three fundamental approaches: first, "smart" surveillance to coordinate surveillance with risk assessment for animals and people, focusing on the places, communities, and animal–human interfaces where evidence shows that emerging diseases are likely to originate; second, basic and translational research informed by smart surveillance to identify priority pathogens, enhance pandemic preparedness, and design better prototype vaccine and therapeutic platforms; and third, governance structures and policy measures to prevent future EIDs by reducing the influence of factors that drive spillover risks from wildlife or farmed wild animals to people.

## The Rationale for Smart Surveillance Coupled with Epidemiologic Risk Assessment

Creating Targeted Smart Surveillance. Global trends in disease emergence (2, 6) and the high diversity of viruses in wildlife with spillover potential (16, 51) indicate that the next pandemic will likely be caused by a novel virus emerging where animal–human interfaces are most expansive. Two strategies, systematically applied, are necessary to effectively preempt spillover: 1) surveillance targeted to the locations where spillover is most likely and 2) coordinated surveillance of wildlife, farmed wildlife, domestic animals, and people who have high contact with animals (Box 4). These are also the pillars of One Health (52).

Smart surveillance targeted to high-risk animal-to-human interfaces in EID hot spots, especially regions undergoing land use change and where communities engage in occupations and activities that increase human–wild animal contact, could reduce surveillance costs and help identify early cases of new syndromes and spillovers (53). Selective sampling of wildlife host taxa and farmed animals serving as reservoirs (16, 51) and introduction of broad-range PCR or NGS for virus discovery would improve effectiveness and provide sequence data to better tune diagnostics. Surveillance must be agile; responsive to technological advances that increase throughput, sensitivity, and specificity; rapidly report on-site testing; and integrate with networks employing artificial intelligence (AI) predictive tools. Similarly, serological diagnosis could broaden to the genus or subgenus level using conserved antigens or multiplex serology introduced for

Box 4. Elements of a smart surveillance system.

- Surveillance targeted to wildlife, domestic and farmed animals, and people at high-risk animal-to-human spillover interfaces and engaged in high-risk activities in emerging disease hot-spot regions
- Diagnostic tests suitable for field use with high sensitivity and specificity using advanced sequencing and serology applied to known wildlife reservoirs, amplifier hosts, and selected environmental samples
- Syndromic, virological, serological, and behavioral risk surveillance of people with occupational or other regular contact with known reservoir or amplifier hosts
- Global networks to share data and relevant clinical and laboratory samples
- Risk assessment methods to identify viruses likely to be high, medium, or low risk for emergence and focus resources on the most likely emergence threats.

sarbecoviruses (54) or "panvirus" platforms, such as VirScan phage display libraries or peptide array platforms (55).

PCR-based surveillance of sewage effluents, successfully used during COVID-19 (56), could be applied to animal waste from manure pits for farm animals or effluents from live animal markets. Innovative sampling (dust, market surfaces, rope-based oral sampling) could further increase coverage. A pilot study in the Singapore public transportation system to monitor bioaerosols successfully detected circulating pathogenic viruses (57). Improved methods integrated with environmental DNA monitoring of the wildlife trade and optimized risk assessment and predictive models could identify which pathogens and animal hosts to focus on (58).

Novel viruses discovered in broad surveys will need to be characterized using a risk assessment framework (51, 59), just as the Influenza Risk Assessment Tool and the Tool for Influenza Pandemic Risk Assessment are used to assess the risk that novel influenza A viruses can transmit among people ("emergence risk") and cause outbreaks ("impact risk") (60). High-risk strains are reviewed by the One Health Quadripartite Group (WHO, the World Organization for Animal Health [OIE], the Food and Agriculture Organization [FAO], and the United Nations Environment Program [UNEP]) to optimize regional vaccine seed strains. A similar approach is being developed for other prespillover potentially zoonotic viruses (https://spillover.global/) (16, 61).

Smart surveillance must ensure that responses are rapid and coordinated when signals are detected, although the diversity of stakeholders and potentially competing interests or priorities remain challenges to overcome. Reference laboratories to identify priority virus families and available funding to support and coordinate veterinary, medical, and public health laboratories are essential (62). This requires information technology capacity to collect, integrate, and evaluate big datasets from sentinel populations. Collecting data without the ability for rapid analysis not only fails to generate actionable information but is a disincentive to pursue and improve the systems. A formal funded global repository and biobank are also essential to collect, store, and share virus isolates and reagents, with tools and protocols to support the development of sensitive, specific diagnostics and countermeasures when variant or new pathogens emerge. If adopted more widely, smart One Health surveillance that includes animal and human sampling at interfaces of heightened spillover risk will need enhanced integrated biosafety and biosecurity measures to address the potential of field and laboratory infections during surveillance programs and to rectify the current lack of standardized protocols, in particular for field sampling of wildlife.

**Proof of Concept.** Sykdomspulsen (Disease Pulse) in Norway is a real-time One Health surveillance system to collate laboratory data from humans, animals, and farms with diagnostic codes from physician visits and weather data for disease outbreak forecasting (https://aca.pensoft.net/article/68891/). The European Commission's Versatile Emerging Infectious Disease Observatory is also developing EID early-warning tools (https://www.veo-europe.eu). The United States Agency for International Development (USAID) PREDICT program's enhanced prepandemic One Health surveillance capacity remains a resource for future expansion (15, 63). Novel pathogen discovery in wildlife has identified bat SARSr-CoVs recognizing human ACE2 (25) used to test the broad efficacy of candidate vaccines, monoclonal antibodies, and therapeutics against SARS-CoV-2 and SARSr-CoVs and generate proof-of-concept data for "universal" CoV vaccines (*SI Appendix*, Table S7).

**Potential Risks of Smart Surveillance.** Surveillance can pose risks of accidental infection for personnel sampling, testing, and analyzing biological samples, even though they are trained and required to use personal protective equipment (PPE). Clinicians caring for sick people or animals, workers involved in farming and trading wildlife, and especially tourists visiting bat caves are likely to be less prepared and at higher risk for exposure and pathogen spillover. Exposure risk in the laboratory is far more manageable and reducible by cross-disciplinary training and oversight, adherence to standard operating procedures, use of appropriate PPE, modern containment laboratory engineering and equipment, and environmental and individual health monitoring.

## Research to Enhance Pandemic Preparedness and Develop Broad Spectrum Vaccines and Therapeutics

Vaccines are central to reducing pandemic consequences, and their development requires long-term research investments, exemplified by the importance of prior platform vaccine research to enable the rapid development of safe and effective SARS-CoV-2 vaccines. Access to research tools also permitted evaluation of therapeutics developed for other pathogens, such as Remdesivir, as therapy for SARS-CoV-2. Some also show efficacy against "prepandemic" bat CoVs, such as WIV-1 and MERS-CoV (*SI Appendix*, Table S7). Smart surveillance can inform preparedness research and development (R&D) by identifying viral targets with high emergence potential for vaccines and therapeutics before an outbreak emerges (64). More platform technologies for additional families of potentially epidemic pathogens would speed product R&D for a newly emerging threat, even if not timely enough to mitigate the first wave. This is why current enthusiasm for platform technologies must not detract from continuing One Health efforts to reduce the risk of emergence itself.

Vaccination of animal reservoirs can reduce threats to people: for example, oral baits have been used to vaccinate wild raccoons against rabies (65). Proposed self-disseminating vaccines for wildlife might reduce the risk of spillover of other zoonotic pathogens (66). Immunization of critical amplifier hosts could potentially limit virus evolution toward enhanced transmission or virulence. Examples include vaccinating poultry or swine for emerging animal influenza A strains or camels for MERS-CoV in endemic countries (67).

Given the rise of vaccine hesitancy and the politicization of COVID-19 responses in the United States, Europe, and many other countries, research into how people access and process scientific research findings, public health advice, misinformation, and disinformation is critical (40, 62, 64).

## Pandemic Prevention by Reducing the Underlying Drivers of Spillover Risk and Spread

Wildlife farming, trade networks, live markets, and expanding domestic livestock production are sources and drivers of

EIDs (68). Permitting current wildlife farming and trade to continue indefinitely is a high-risk and unsustainable policy that urgently needs rethinking. However, incentives to consume wildlife are often deeply rooted in centuries-old cultural practices, so policies to modify rather than ban this system are more likely to succeed in reducing spillover risk. Interventions informed by smart surveillance at relevant interfaces include behavior change programs, risk education, more effective communication, enforcement of regulations, and incentives for more sustainable food production. Expansion of wildlife farming and trade is often linked to economic growth in developing countries that are also EID hot spots (8), and the disconnect between profits driven by private sector enterprise and deferred health costs primarily borne by the public sector can make prevention policies ineffective (69). Systematic long-term efforts to explain their importance to politicians and the public will be critical.

Global consumption patterns often exploit natural resources in EID hot spots for the benefit of those living far away, linking one country's consumption to another's disease burden, such as wildlife farming in Asia to produce fur for fashion products largely sold elsewhere. This challenge is reflected by the Chinese Government's decision to close all wildlife breeding farms for food animals on 24 February 2020 but specifically exclude wild animals farmed for the fur trade, including mink, raccoon dogs, and foxes, all susceptible to SARS-CoV-2 infection. Policy changes based on scientific evidence from smart surveillance, understanding optimal intervention points, and partnerships with economically important industries to reduce spillover potential would likely benefit public health. To be most effective, this ultimately requires broad social transformative changes in behavior and consumption patterns.

A Biosecure Wildlife Farming Industry. Hunting and trade in wildlife for food, fur, and medicinal purposes are ancient activities fundamental for human survival. Recently and particularly in Southeast Asia, local, small-scale trade in wildlife by individuals has transitioned to coordinated, international trade networks, with rapid growth of wildlife farming for the live animal trade to alleviate poverty in rural populations (11). A vast network of wildlife farms and markets employed 14 million people in China alone in 2016 (12). COVID-19 has heightened awareness of the scale of the international trade in valuable animals, both legal and illegal. The United States is the largest single market for wildlife pets, importing millions of live animals from EID hot-spot countries without effective surveillance or regulatory oversight (10). The zoonotic spillover of SARS-CoV-2 in Hong Kong from pet hamsters to humans illustrates the importance of gaps in oversight (42). The scale of these activities escalates concerns for future outbreaks of novel diseases and the urgent need to prioritize a "harm reduction" strategy permitting the trade of species when it can be done safely. There are critical control points in the farming and trade of wildlife to prevent wildlife spillovers (Box 5). Promoting market rest days, enforcing existing restrictions on overnight boarding of animals to allow for cleaning but permitting the preparation of products from unsold animals, restricting direct retail sales of live birds, and introducing poultry vaccination programs have reduced economic losses from avian influenza A in Hong Kong (70). Elsewhere, the dearth of information about health and safety inspections of live animal markets, failures of surveillance and regulatory enforcement, and poor reporting of health threats in markets and wildlife farms that supply them severely impede informed policy decision-making. OIE recently launched the Wildlife Health Framework to improve the surveillance, early detection, notification, and management of wildlife diseases and is developing standards to operationalize it. (https://www.woah.org/fileadmin/Home/eng/Internationa_Standard_Setting/docs/pdf/WGWildlife/A_Wildlifehealth_conceptnote.pdf).

**Box 5. Policy options to control wildlife spillovers.**

- Ban/regulate high-risk animal species known to act as reservoirs or amplifier hosts from farms and markets
- Enact stricter laws to prevent mixing of wild-caught and captive bred wildlife
- Increase biosafety procedures in wildlife farms and markets
- Enhance inspection mechanisms and enforce policies and penalties for violations
- Smart surveillance of wildlife hunters, farmers, transporters, and live market workers
- Close regulatory gaps, and increase surveillance for the global pet trade
- Define and coordinate regulatory responsibility for wildlife farming and the wildlife trade
- Change traditions for wildlife consumption by education and altering market incentives and organization.

Reducing the Threat of Disease Emergence via Land Use Change. Land use change from logging, mining, road building, agricultural expansion, and human settlements drives over 30% of EIDs (68). They also alter wildlife movement and may create new overlapping habitats that can foster close contact of previously isolated species. While land conversion can yield short-term economic growth, increased food production, infrastructure investment, and tax revenue, they fail to account for the loss of ecosystem services that forests provide to the whole community, including the survival of pollinators, pest removal, and renewable fuel and fiber (11). Economic benefits are further reduced when linkages to known disease outcomes and associated costs are assessed (69). Working with the private sector, in particular the extractive industry, to reduce contact with wildlife at project sites improves worker health and likely translates to higher productivity from healthier workers.

Global Governance and Stewardship. Governance is essential for progress, especially when many interests with varying resources or power are involved. Control over regulations to reduce the threat of zoonotic EIDs or determine R&D priorities is usually closely guarded by governments and the private sector, making it difficult to ensure broad global political or financial buy-ins; sharing of information, samples, or intellectual property; or access to affordable vaccines or therapeutics. There is no obvious governance model to guarantee basic fairness principles, such as inclusivity, equity in collaborations and benefit sharing, and fair and rational distribution of products based on global impact.

Box 6. Principles of good governance.

- Broad participation
- Procedural framework
- Transparency
- Responsiveness to stakeholder needs
- Consensus building
- Equity and inclusiveness
- Effectiveness
- Accountability.

Quadripartite (WHO, FAO, OIE, and UNEP) initiatives could become a One Health leadership model, but their limited resources; authority to act; and legal, policy, and knowledge gaps must be overcome. The eight principles of good governance promoted by the UN Economic and Social Commission for Asia and the Pacific can frame these discussions (Box 6) (http://www.unescap.org/sites/default/files/good-governance.pdf).

Existing science and policy interfaces, such as the Intergovernmental Science-Policy Platform for Climate Change and the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES), can also serve as models. Over time, they have helped elevate climate change and biodiversity loss to the political agendas of most countries through independent science-based advice while creating societal awareness of global threats to a sustainable future. A similar standing structure focused on pandemic preparedness and prevention is already being framed by the IPBES Pandemic Report on the linkages between pandemics and biodiversity loss (11). Early discussions on the need for a Global Pandemic Treaty could pave the way for multisectoral One Health coordination mechanisms among signatory countries to improve pandemic preparedness (https://www.who.int/news/item/01-12-2021-world-health-assembly-agrees-to-launch-process-to-develop-historic-global-accord-on-pandemic-prevention-preparedness-and-response). An effective solution must provide incentives for participation as well as enforcement mechanisms where necessary. The Group of Twenty (G20) has called for One Health Resilience (https://www.oie.int/en/striving-for-one-health-resilience/) and for One Health to be incorporated as a key approach to global health (https://www.oie.int/en/g20-ministers-of-health-reaffirm-the-urgent-need-to-address-global-health-under-a-one-health-approach/). The G20 High-Level Independent Panel on Financing the Global Commons for Pandemic Preparedness and Response has recommended at least US $75 billion in public sector investments to address the gaps in pandemic prevention and preparedness (https://nam.edu/g20-high-level-independent-panel-releases-report-on-financing-the-global-commons-for-pandemic-preparedness-and-response/). The time to energize these processes is now when the tragedy of COVID-19 continues to confront the public and politicians.

## Conclusions

Infectious diseases will continue to emerge or reemerge. RNA viruses, especially those with a propensity to mutate and/or recombine among strains affecting multiple host species (influenza A viruses and CoVs), pose a "clear and present danger." History shows that we have failed to heed the lessons from past EIDs, and science shows that the rate of emergence is accelerating. An integrated One Health strategy going forward offers the potential to mitigate emergence and implement rapid response when necessary to reduce impact.

## Recommendations

The following recommendations for translating what we have learned into action reflect an underlying core principle that the capacity for prevention and preparedness is as important as the capacity for response. This can only be achieved through the adoption and application of a One Health approach.

Smart Surveillance to Identify High-Threat Groups of Pathogens.

1) Identify "hot spots" for potential zoonotic pathogen emergence and implement targeted surveillance at the animal–human interfaces at these sites.
2) Improve methodologies for safe surveillance (e.g., multiplex or systems serology; broad-range PCR; application of sewage and air surveillance; and coordinated regional, national, and local laboratories serving in areas of high risk).
3) Innovate new strategies and methods for risk assessment of surveillance data (e.g., human organoid cultures, ex vivo explant cultures of human lung, or AI methodologies to assess relative risks).

Preparedness and Translational Research.

1) Invest in preparedness R&D to develop broad spectrum antiviral and vaccine strategies and diagnostics suitable for field use for priority viruses and virus families with high epidemic or pandemic potential.
2) Streamline strategies and build capacity for clinical trials, licensure, and manufacture of countermeasures (vaccines, antivirals).
3) Understand pathogenesis of potential high-threat pathogens to better define correlates of protection and reduce disease severity by targeting adverse pathogenic innate and cellular host immune responses.

Reduce the Drivers for Spillover and Spread.

1) Understand the epidemiological/value chain/behavioral drivers of EID emergence and implement evidence-based interventions for generic "risk reduction at the source."
2) Develop economic, cultural, and social incentives to minimize contact at human–wildlife interfaces in rural areas and commercial markets, diminish trading in live wildlife and their products, and calculate the emerging disease–linked health impacts of land use and climate change to provide incentives for sustainable development.
3) Strengthen awareness and education of scientists, other stakeholders, and society to the need for transformative behavioral changes to mitigate drivers that contribute to pandemic emergence, biodiversity loss, and the depletion of ecosystem resources.

Counter Misinformation and Disinformation about the Prevention and Control of Emerging Diseases.

1) Support interdisciplinary research on the genesis of misinformation and disinformation and develop robust countermechanisms that emphasize collaboration and dialogue among diverse scientists, professional societies, academies, government agencies, the private sector, nonprofits, non-governmental organization (NGOs), and the public.
2) Create organizations that provide advice, legal assistance, and other forms of aid to support scientists under attack from disinformation and politically motivated attacks.
3) Design and promote school-based and other science education programs to improve public understanding of the scientific method; what it can tell us about complex issues, such as pandemics; and where to find and identify trustworthy information.

Strengthen One Health Governance and Science.

1) Create and strengthen an inclusive multistakeholder One Health–based governance at all national, regional, and international levels for pandemic preparedness and response.
2) Increase funding for cross-disciplinary collaborative research aimed at closing knowledge gaps across the One Health continuum that fosters a truly transdisciplinary and internationally based approach to EIDs.
3) Incorporate the One Health approach into all national, regional, and international public health; animal; and environmental health strategies, including a focus on increased south–south collaboration, inclusion of indigenous knowledge, public and private sector expertise, and participation of civil society.

Data Availability. This work involved review of data that are already available publicly.


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