https://doi.org/10.31631/2073-3046-2026-25-1-4-11

Genomic Epidemiological Surveillance and Epidemic Forecasting

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Abstract

Relevance. *The current global epidemiological situation is characterized by a highly challenging epidemiological situation caused by the combination of emerging biological challenges and persistent traditional threats, necessitating the development and implementation of innovative approaches to epidemiological surveillance and to forecasting the epidemic process of infections caused by known and potential pathogens.* ***Aims.*** *To substantiate a strategy for proactive assessment of epidemiological risks based on genomic epidemiological surveillance in order to improve epidemic prevention and optimize control measures.* ***Conclusion.*** *The modern paradigm of predictive epidemiological analysis relies on integrating pathogen genome data with assessment of its evolutionary potential and the host epigenetic response, which serves as a universal early marker of infection, including infections caused by previously unknown pathogens. Integration of these data with digital platforms enables a systematic, multi-level genomic epidemiological surveillance framework aimed at preventing possible epidemics and pandemics and at developing and optimizing public-health response strategies.*

Keywords: *genomic epidemiological surveillance, VGARus platform, genomic and epigenetic technologies, digital platforms, biosafety, proactive epidemic forecasting*

No conflict of interest to declare.

For citation: *Akimkin VG. Genomic Epidemiological Surveillance and Epidemic Forecasting. For citation: Epidemiology and Vaccinal Prevention. 2026;25(1):4-11 (In Russ.). https://doi:10.31631/2073-4-11*

The contemporary global epidemiological landscape is characterized by persistent tension driven by the convergence of emerging biological challenges and enduring traditional threats, as evidenced by the recurrent occurrence of epidemics and pandemics. This trajectory is largely shaped by the rise of emerging and re-emerging infectious diseases, whose causative agents are either insufficiently characterized or rapidly altering their biological properties. Against the backdrop of profound ecological, climatic, and anthropogenic transformations, pathogens increasingly overcome interspecies barriers; it is therefore unsurprising that a substantial proportion of infectious diseases are of zoonotic origin. Urbanization, disruption of natural habitats, intensification of agriculture, and the unprecedented scale of global mobility and trade further amplify the epidemic process. Collectively, these socio-environmental transformations create optimal conditions for expanding pathogen diversity and accelerating adaptive evolution – developments that have become critically significant for public health systems worldwide.

In 2024, WHO published an updated list of priority pathogens spanning nearly 30 families – an important anticipatory step that reflects the global community's commitment to strengthening preparedness for future pandemics. The prioritization process considered available evidence on transmission mechanisms, virulence, mutational activity, and the existence of validated countermeasures [1]. It should be emphasized that earlier WHO lists (2017 and 2018) ranked specific pathogens primarily by their capacity to cause public health emergencies of international concern [2]. While these lists served as useful guidance for basic and applied research, they had a substantial limitation: they largely ignored the pathogen's intrinsic nature and variability. This hampered the development of truly flexible and adaptive strategies for assessing pandemic threats. In the 2024 WHO framework, this limitation can be considered largely addressed through a major methodological shift: all

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** Vasily G. Akimkin, Academician of the Russian Academy of Sciences, MD, PhD, Professor, Honored Doctor of the Russian Federation, Laureate of the Government of the Russian Federation Prize in Science and Technology, Laureate of the Government Prize in Medical Science, Director of the Federal Budgetary Institution of Science «Central Research Institute of Epidemiology» of Rospotrebnadzor. 3A Novogireevskaya St., Moscow, 111123, Russian Federation © V. G. Akimkin* known pathogen families are assessed under the premise that any of them – including those currently classified as low-risk – may become the source of a future pandemic. This approach recognizes that evolutionary processes, whether genetic change or variation in ecological conditions, can transform pathogens of minimal current epidemiological relevance into major threats [1]. In addition, a key innovation was the introduction of so-called prototype pathogens – model representatives selected from families with high pandemic potential for in-depth investigation of the relevant taxonomic groups [3]. Selection criteria were stringent and included epidemiological significance, the level of knowledge about pathogenesis and replication, and, importantly, the availability of validated animal models for studying human disease [1]. This proactive strategy contrasts with more traditional approaches focused on developing preventive and response countermeasures against narrowly defined pathogens – a limitation that became particularly evident during rapidly unfolding pandemics such as COVID-19 [4].

Beyond these changes, the 2024 priority pathogen list introduced “Pathogen X” – a hypothetical infectious agent capable of becoming a pandemic threat in the future [5]. Expert consensus suggests that likely etiological candidates for such an unknown but high-impact infection are RNA viruses, which are characterized by high mutagenesis rates, substantial evolutionary potential, and the capacity for rapid epidemic spread. Coronaviruses and orthomyxoviruses are often cited among such candidates [6,7].

Global epidemiological dynamics are shaped not only by the emergence of new threats. In recent years, long-known infections such as tuberculosis, cholera, and malaria – as well as influenza, measles, and orthopoxvirus and arboviral infections – have also undergone notable transformations, largely driven by ongoing changes in the biological properties of their etiological agents and by shifts beyond their former ecological ranges. Additional drivers include the widespread rise of resistance to antimicrobial and antiviral agents, ecosystem evolution and disruption, and the effects of natural disasters, among others. Together, these factors markedly increase the likelihood of outbreaks even in areas previously considered epidemiologically stable [8]. The coexistence of new challenges with traditional threats creates a complex and volatile epidemiological environment that requires continuous monitoring and adaptive prevention and control strategies.

Under these conditions, the effectiveness of classical epidemiological surveillance systems – based on phenotypic diagnostics, case reporting, clinical indicators, and conventional laboratory testing – becomes limited. The core problem is that such systems do not provide timely information on rapidly evolving pathogens capable of altering key biological properties within very short timeframes [9]. This limitation became particularly apparent during the COVID-19 pandemic, when the exceptionally high mutational variability of SARS-CoV-2 highlighted the need for fundamentally new approaches both to surveillance itself and to forecasting the epidemic process of a novel infection [7,10,11].

It is important to note that the domestic epidemiological surveillance system has undergone a long evolution – from routine case registration to multilevel structures with complex functionality. For much of the 20th century, surveillance focused primarily on long-term and annual trends in morbidity and mortality, as well as on microbiological and serological monitoring. Spatial-temporal patterns were identified, data on the structure of morbidity and its distribution across territories, exposures, and risk groups were accumulated, and management decisions were derived on this basis [12]. This model functioned effectively while pathogen biology changed relatively slowly and global population mobility remained limited. In the second half of the century, laboratory diagnostics advanced substantially with the introduction of immunoassays (including various ELISA formats) and molecular methods – polymerase chain reaction (PCR), sequencing, hybridization, and others. These innovations expanded epidemiological research capacity, improved pathogen identification, and enabled mapping of circulation pathways [13]. Nevertheless, the approach remained inherently inertial, as it targeted already known pathogens and did not allow rapid, comprehensive assessment of changes in pathogen biology at the population level.

A key milestone in the evolution of surveillance in the 21st century was the emergence of high-throughput sequencing, also known as next-generation sequencing (NGS). Its principal advantage over earlier Sanger sequencing is the shift from analysis of individual loci to whole-genome interrogation. NGS enables direct pathogen identification without prior assumptions about its nature. Unlike traditional methods, NGS makes it possible to track the evolution of infectious agents, reconstruct phylogenetic relationships, detect mutations and variants of epidemiological significance, and identify cryptic transmission clusters [14]. It also supports monitoring of drug-resistance genes down to specific nucleotide substitutions.

With the onset of the COVID-19 pandemic, genomic technologies became the core instrument of global epidemiological surveillance. Rapid large-scale sequencing of SARS-CoV-2 made it possible to determine the structure of its genome in a short time. Sequence data enabled reconstruction of evolutionary dynamics, identification of variants with increased transmissibility and pronounced immune-escape mechanisms, and inference of geographic spread trajectories [15,16]. In 2022, WHO formally established the term "genomic epidemiological surveillance" in its Global Strategy for Genomic Surveillance for Pathogens with Pandemic and Epidemic Potential. The strategy aims to establish a unified concept for applying genomics as a powerful complementary tool within public health, particularly for preparedness and response to public health emergencies of international concern [17].

The COVID-19 pandemic provided a strong impetus for molecular genetic research, leading to the development of fundamentally new platform solutions that integrate NGS technologies, bioinformatic tools for data analysis and interpretation, and digital systems for integration and visualization of results.

Pursuant to the Government of the Russian Federation Order of March 23, 2021 No. 448 on establishing a unified information center for analysis of the epidemic situation and tracking circulating coronavirus genetic variants in the country, the Russian Virus Genome Aggregator of Russia platform (VGARus) was created at the Central Research Institute of Epidemiology of Rospotrebnadzor [18]. VGARus serves as a centralized repository of genomic data, integrating them with epidemiological information and providing analytical tools to assess pathogen genetic diversity. Priority areas include collection and aggregation of molecular biological characteristics of viral and bacterial pathogens, analysis of genetic variability, and study of temporal dynamics of circulating genetic variants across the Russian Federation [19]. These tasks are supported by neural network and machine-learning methods, improving the efficiency of processing large datasets and the quality of analytical outputs.

The platform has evolved into a key instrument for countering the SARS-CoV-2 pandemic in the Russian Federation. It enabled tracking of the spatial-temporal dynamics of COVID-19 incidence, facilitated detection of new viral variants and significant mutations, and thereby provided a scientific basis for developing effective diagnostic assays and for evidence-informed public health decision-making. Subsequently, VGARus was expanded and adapted to support genomes from a broad spectrum of pathogens. As of January 2026, the platform contains data on more than 450,000 nucleotide sequences, including over 270,000 complete genomes and 180,000 genome fragments. Pathogens represented include SARS-CoV-2; influenza A and B viruses; hepatitis A, B, C, D, and E viruses; enteroviruses A-D; noroviruses; cytomegaloviruses; papillomaviruses; measles and varicella viruses; Salmonella spp.; and other agents. The metadata comprise more than 20 anonymized variables, including epidemiological history. More than 80 organizations across different institutional jurisdictions participate in sequencing and data submission, ensuring scalability and system resilience. Upload workflows support sequences for more than 100 pathogens, and this list continues to expand as the national surveillance system develops [7,16].

The success of VGARus in enabling deposition and classification of genomes from infectious and parasitic disease agents underscores its high value for epidemiological surveillance, yet it does not exhaust the platform's functional potential. Under current conditions, a key priority is to use genomic technologies not only for monitoring but also for forecasting the epidemic process [20]. This includes estimating the likelihood of adaptive variants arising under natural selection, modeling evolutionary trajectories of pathogens, and predicting their potential epidemiological significance [21]. For example, the analytical capabilities of VGARus were used to anticipate increased COVID-19 incidence in the summer of 2022 and at the beginning of 2023; both surges were associated with the emergence of Omicron subvariants BA.5 and XBB, respectively [16,22]. This enabled health authorities to promptly adjust response measures.

The contemporary paradigm of predictive epidemiological analysis is grounded in integrating data on the pathogen genome with information on the host epigenetic response [23]. Genomic studies enable detection of new pathogen variants, assessment of their selective advantages, and reconstruction of evolutionary trajectories. Epigenomic approaches, in turn, capture specific changes in the regulation of human gene activity arising at early stages of infection. The combined pattern of these changes may be considered a universal early marker of infection, including infections caused by previously unknown pathogens [24].

Among the best-characterized mechanisms of host epigenetic regulation during infection is the remodeling of DNA CpG-site methylation profiles, which can activate or suppress gene expression. This reflects both viral attempts to modify the cellular environment to facilitate replication and the activation of host protective pathways. In Russia, such studies rely on national biotechnological solutions, including the GlaI enzyme, which enables high-precision mapping of methylated DNA regions and the construction of epigenetic signatures associated with pathogen exposure [25].

Joint use of genomic and epigenomic data provides a methodological foundation for building early, proactive systems for epidemic forecasting and prevention. This approach helps identify molecular mechanisms of pathogenesis, assess the potential epidemic impact of pathogens, and prioritize promising therapeutic targets. As a result, genome-epigenome integration shifts epidemiological surveillance from a predominantly observational model toward a predictive framework for managing biological risks [23].

The genomic-epigenomic direction aligns naturally with the concept of self-regulation of parasitic systems developed by Academician V.D. Belyakov. This theory, recognized as a scientific discovery, conceptualizes interpopulation parasite-host relations as a system governed by internal self-regulatory processes. Its key principles include genotypic and phenotypic heterogeneity of parasite and host populations, dynamic variability of their biological properties, phase-like self-restructuring of parasite populations underlying the uneven development of the epidemic process, and regulatory influences of social and natural factors that can accelerate or slow phase transitions of the epidemic process [26]. The development of innovative molecular biological technologies not only provides high-confidence support for the self-regulation theory but also deepens its interpretation. The focus shifts from documenting events that have already occurred to identifying internal determinants that shape probabilistic trajectories of epidemic evolution [27]. In this context, genomic and epigenomic data act as indicators of the dynamic “pathogen-host” system state. They capture deviations from equilibrium and allow prediction of the direction of change. In terms of modern technological language, sequencing outputs and early shifts in DNA methylation and transcriptional activity serve as molecular markers of phase changes in the heterogeneity of interacting pathogen and human populations. Leveraging such integrated signals for early-stage infection markers requires tools capable of collecting, processing, and interpreting heterogeneous data in near real time. This is where digital platforms and artificial intelligence methods become central, linking complex biological signals to practical management of the epidemic process and laying the foundation for a new generation of surveillance systems. Integration of molecular biological findings with mathematical modeling enables adaptive forecasting systems that update as new data arrive. Through this integration, genomic epidemiological surveillance evolves from a monitoring method into a powerful analytical tool for managing the epidemic process. A central role in this system is played by digital bioinformatic platforms that support streaming transfer of genetic data and automated updating of epidemiological models. Their task is to provide a technological framework for integrating sequencing data with analyses of pathogen spread dynamics [28,29]. These platforms must not only store data, but also perform algorithmic sequence processing, enabling rapid detection of new variants, assessment of their spread rates, and real-time adjustment of model parameters.

Analysis of genomic and epigenomic data makes it possible to characterize key pathogen properties, including mutation rates and variability, immune-escape potential, and features of interaction with the host organism, as well as host epigenetic regulatory mechanisms and the strength of immunological memory. These parameters can then be embedded into epidemiological models, including classical SEIR structures, phylodynamic models, multi-strain interaction models, and agent-based simulators [24,30].

Accordingly, models can represent both incidence dynamics and the microevolutionary processes that determine the probability of new outbreaks. This approach provides a fundamentally different level of sensitivity for surveillance systems: it enables detection of changes in mutational dynamics and epigenetic patterns at early stages that precede clinical manifestations. As a result, genomic epidemiological surveillance of infectious disease agents transforms into an early-warning system for epidemic threats. A major acceleration in analytical capacity is achieved through the adoption of artificial intelligence and machine-learning methods. Deep neural networks are used to identify latent patterns in large sequence datasets, predict the effects of mutations on protein structures, and estimate the probability of variants with higher transmissibility or increased immune evasion [31,32]. Machine learning facilitates classification of genetic lineages, automates recombination detection, and supports forecasts based on early signatures* of adaptive evolution. Moreover, high-performance AI models can act as “digital twins” of epidemics – continuously updated computational models synchronized with real-time sequencing streams and adjusting forecasts of infection spread accordingly [33,34]. This was particularly evident during the COVID-19 pandemic, when big-data analytics and sequencing integrated with AI models enabled prediction of Omicron dominance before epidemic curves reflected its exponential growth [28,35].

A new paradigm of epidemic forecasting is emerging through the combined use of digital platforms, artificial intelligence, mathematical modeling, and genomic and epigenetic information. This paradigm links pathogen evolutionary mechanisms to morbidity dynamics and supports adaptive risk-management systems, enabling more precise countermeasure strategies at both global and local levels.

Genomics-based epidemic forecasting is an actively discussed topic in the international literature. Wilson C.N. et al. (2023) proposed the concept of “genomics on the move,” describing the transformation of surveillance under the influence of high-throughput NGS. According to the authors, mobile sequencing technologies, together with integration into global platforms such as Nextstrain and GISAID, create a closed loop: “sequencing-analysis-modeling-decision.” This enables near real-time insight into mutations and pathogen evolution and turns genomic epidemiological surveillance into the backbone of early-warning systems for dangerous pathogen strains [28]. This concept proved particularly valuable during the COVID-19 pandemic, when global sequencing networks rapidly detected new SARS-CoV-2 variants, including Alpha, Delta, and Omicron, enabling assessment of their epidemic potential and interpretation of regional differences in epidemic curves. Similar approaches are used for influenza: annual monitoring of genetic diversity of influenza A and B supports forecasting of dominant variants and provides an evidence base for selecting seasonal vaccine compositions [28].

A further step in forecasting methodology is associated with models that explicitly couple evolutionary and epidemic processes, as illustrated by Cárdenas et al. (2022). Their simulation system Opqua enables analysis of the emergence and fixation of new adaptive genetic lineages and assessment of the likelihood of strains with increased transmissibility. Opqua thus opens the way to using pathogen sequencing not merely to track the spread of mutant forms, but to construct probabilistic scenarios of epidemic development that account for changing pathogen properties [36]. This approach has proven informative for COVID-19, since mutations in the SARS-CoV-2 spike (S) protein are closely linked to changes in pathogenicity and immune escape. Opqua-like models help estimate the probability of pandemic variants and subsequent incidence surges.

Findings reported by Espinoza B. et al. (2023) in the Proceedings of the National Academy of Sciences are of particular importance. Their work demonstrates that genomic epidemiological surveillance plays a decisive role in identifying new pathogen variants not only in terms of molecular characterization, but also in pinpointing the timing of their emergence and dissemination in populations.

This makes it possible to provide early warning of epidemic upswings in incidence before they expand into full outbreaks. The authors concluded that integrating genomic surveillance with analyses of pathogen evolution and with modeling of intervention effectiveness makes it feasible to predict competition dynamics among strains with different effective reproduction numbers and cross-immunity. In addition, such approaches allow identification of optimal time windows for preventive measures capable of preventing epidemic increases in morbidity [7,16,22,30].

Comparable forecasting potential was demonstrated in a recent study by Zarebski A. et al. (2025). Using the BEAST2 Timtam model, the authors showed that combining sequencing data with incidence time series makes it possible to estimate dynamics of the reproduction number and infection prevalence, reconstruct epidemic trajectories, and produce accurate short-term forecasts of pathogen spread. The approach was successfully applied to evaluate the rate of spread and turnover of SARS-CoV-2 variants. Data generated with BEAST2 Timtam enabled reconstruction of the temporal structure of epidemic waves and forecasting of the probability of subsequent upswings driven by highly antigenically variable pathogens, including influenza A(H3N2) and A(H1N1) viruses [35].

The importance of integrated analysis across multiple data sources is emphasized in a review by Vashisht V. et al. (2023). The authors show that applying machine learning and AI methods to genomic, clinical, geographic, and social information can help predict interspecies transmission and the emergence of novel pathogens, as well as their likely dissemination routes, thereby forming the basis of multi-level

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Signatures are distinctive identifiers or feature patterns employed to identify objects, datasets, or functional elements.

infection prediction systems [32]. This is particularly relevant for influenza, which has high zoonotic potential. Genomics-based models can estimate the likelihood of transmission from birds or pigs to humans. However, implementing such models requires enabling infrastructure, as discussed by Pronyk P. et al. (2023), who advocate developing regional sequencing hubs, training specialists, and standardizing data – key prerequisites for operational forecasting models [38].

Duval A. et al. (2023) expanded the methodological base for forecasting by proposing dynamic thresholds of genetic distance between pathogen isolates. This approach can support identification of new epidemiological clusters and prediction of their subsequent development, as well as estimation of outbreak scale and duration through neural-network models of pathogen mutational processes [38].

In summary, high-throughput sequencing has opened access to vast volumes of genomic data and has become a key resource for forecasting the epidemic process. Tracking genetic changes over time enables identification of evolutionary trends, assessment of selective advantages of specific mutations, and accurate prediction of the subsequent spread of infectious variants with high specificity. Fitness models, together with phylogenetic approaches, for example, can forecast frequencies of circulating SARS-CoV-2 lineages based on temporal series of genomic sequences [39,40]. Thus, NGS has evolved from a tool for looking backward into a source of information about future pathogen evolutionary trajectories.

The power of forecasting models increases substantially when human epigenomic data are incorporated, as these data influence susceptibility and immune reactivity. Epigenomics captures dynamic features – chromatin architecture, RNA and DNA methylation patterns, histone modifications, activity of regulatory elements – that together shape individual immune-response profiles. Even short-term exposure to viral pathogens can induce long-lasting remodeling of the epigenetic landscape, leading to altered reactivity of innate immune cells [24]. This additional layer of biological information is important for assessing how specific populations may respond to the emergence of a new genetic variant of a pathogen.

Conclusion

Integrating genomics and epigenomics enables more accurate and anticipatory management of epidemiological risks and provides a foundation for proactive public health decision-making. National genomic surveillance systems have already shown that data on viral variants can be used to adjust vaccine strategies and to evaluate the effectiveness of measures aimed at controlling the spread of infectious diseases [7,16,23,39–41]. When epigenomic profiles are added, it becomes possible to move from universal prevention models to more differentiated and flexible approaches. For example, this may include targeted revaccination of specific population groups and adaptive modification of anti-epidemic interventions during periods when the probability of unfavorable evolution- and epigenetically mediated changes that increase epidemic risk is high.

At present, owing to the efforts of national researchers, the national methodological foundations of epidemiology and the scientific and technological base provide Russia with the capacity to strengthen its position as one of the global leaders in genomic epidemiological surveillance. Advances in PCR methodologies, isothermal amplification (LAMP), CRISPR/Cas editing, high-throughput sequencing (NGS), metagenomic, targeted, and immune sequencing form the scientific and technological backbone of modern epidemiological surveillance in the Russian Federation. The national VGARus platform supports a systematic, multi-level genomic surveillance framework, and integration of these solutions with digital platforms, Big Data technologies, machine learning, and artificial intelligence expands opportunities for forecasting epidemiological risks and reinforces Russia's role in shaping the global architecture of epidemiological security.

Therefore, the use of large-scale genomic sequencing datasets on infectious disease agents in combination with human epigenomic data makes it possible to forecast not only observed trends, but also yet unrealized trajectories of co-evolution between the pathogen and the human immune system. This provides the basis for proactive scenarios to prevent future epidemics and to elevate preventive medicine to a new level.

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Received: 19.12.2025. Accepted: 03.02.2026.