Review

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Big Epidemiology: The Birth, Life, Death, and Resurgence of Diseases on a Global Timescale

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Abstract. Big Epidemiology is an innovative framework that extends the interdisciplinary approach of Big History to understand disease patterns, causes, and effects across human history on a global scale. This comprehensive methodology integrates epidemiology, genetics, environmental science, sociology, history, and data science to address contemporary and future public health challenges through a broad historical and societal lens. The foundational research agenda involves mapping the historical occurrence of diseases and their impacts on societies over time, utilizing archaeological findings, biological data, and historical records. By analyzing skeletal remains, ancient DNA, and artifacts, researchers can trace the origins and spread of diseases, such as *Yersinia pestis* in the Black Death. Historical documents, including chronicles and medical treatises, provide contextual narratives and quantitative data on past disease outbreaks, societal responses, and disruptions. Modern genetic studies reveal the evolution and migration patterns of pathogens and human adaptations to diseases, offering insights into co-evolutionary dynamics. This integrative approach allows for temporal and spatial mapping of disease patterns, linking them to social upheavals, population changes, and economic transformations. Big Epidemiology also examines the roles of environmental changes and socioeconomic factors in disease emergence and re-emergence, incorporating climate science, urban development, and economic history to inform public health strategies. The framework reviews historical and contemporary policy responses to pandemics, aiming to enhance future global health governance. By addressing ethical, legal, and social implications, Big Epidemiology seeks to ensure responsible and effective epidemiological research and interventions. This approach aims to profoundly impact how we understand, prevent, and respond to diseases, leveraging historical perspectives to enrich modern scientific inquiry and global public health strategies.

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Introduction

Diseases are inherently complex, arising from a myriad of interconnected, cascading biological, environmental, behavioral, and societal factors [1,2]. Understanding these determinants and effectively managing diseases necessitates a multidisciplinary approach, involving the collaboration of various fields. These traditionally include basic and translational disciplines (from molecular and cellular biology to genetics, physiology, pathology, and physiopathology), as well as (more) applied ones, like epidemiology, public health, clinical, and clinical public health medicine.

In some circumstances, the comprehension of diseases has leveraged psychology, and, less frequently, social sciences and humanities (from literature to fine arts, history, geography,

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anthropology, and even politic and economics, among others). However, the integration of these disciplines would allow for a comprehensive analysis (and forecasting) of disease dynamics, considering not only genetic predispositions but also evolutionary histories, trajectories, environmental exposures, behaviors, and the impact of policies.

Diseases have, indeed, a history and are deeply intertwined with human history, emerging, evolving, and re-emerging over time. As such, an "ecological" and "population" perspective is crucial, recognizing that individual health is influenced by a complex interplay of various diseases and health conditions — a concept known as pathocenosis [3]. Pathocenosis refers to the coexistence and interaction of different diseases/disease states within a population, shaping the overall health dynamics and epidemiological profile of the community. This concept underscores the importance of considering multiple health conditions and their interactions rather than focusing on individual diseases and factors in isolation.

Recent advancements in genomics, evolutionary biology, and evolutionary medicine have further layered the complexity of disease dynamics. Nearly all genetic variants that influence disease risk have human-specific origins, yet the systems they impact trace back to ancient evolutionary events [4]. Human populations exhibit differences in the prevalence of many common and rare genetic diseases due to their diverse environmental, cultural, demographic, and genetic histories. For instance, the genetic architecture of diseases can vary significantly between populations, influenced by demographic and historical events like bottlenecks, and introgression, slave trade, migrations, intercontinental explorations, military expeditions, wars, and the industrial revolution, which have shaped the genetic composition of human populations. Additionally, evolutionary trade-offs and antagonistic pleiotropy play pivotal roles in disease dynamics. Genes that provide adaptive advantages in certain environments can predispose individuals to diseases in different contexts. For example, alleles that protected against infectious diseases in ancestral environments might increase susceptibility to autoimmune disorders in modern settings. Similarly, traits optimized for reproductive success can lead to increased risk of diseases like cancer or neurodegenerative disorders due to trade-offs in resource allocation, metabolic, and other cellular functions [4,5].

Moreover, considering the historical context of human evolution is essential in understanding disease mechanisms. The evolutionary history of traits, including ancient adaptations and recent changes, can illuminate why certain populations are more susceptible to specific diseases. This historical perspective provides valuable insights into how past environmental pressures and genetic adaptations influence current health outcomes.

Understanding pathocenosis, disease ecology, and, broadly speaking, the evolutionary context of diseases can provide a more holistic view of global public health, guiding more effective interventions and health policies to improve population health outcomes. By integrating diverse perspectives and expertise, we can gain a comprehensive understanding of disease mechanisms, identify at-risk populations, and develop holistic management strategies that address not only the biological aspects but also the social determinants of health. This collaborative approach is essential for improving health outcomes and ensuring effective, sustainable disease control and prevention.

The Big Epidemiology Paradigm

Under these premises, "Big Epidemiology" represents a conceptual extension of Big History [6,7], applying a vast, interdisciplinary approach to understand disease patterns, causes, and effects across human history on a global scale. This comprehensive framework aims to address present and future global public health challenges by viewing them through a broad historical and societal lens. The foundational research agenda for Big Epidemiology begins with mapping the historical occurrence of diseases and their impact on societies over the time. This involves combining historical data (including archaeological findings or historical records), biological data (such as genetic and postgenetic data), and clinical data to trace the origins, spread, and societal impacts of diseases.

Traditionally, this has been done with major infections, like the Black Death, smallpox, and influenza [8–11], but the approach extends to noncommunicable diseases as well, like malignancies

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[12] or sleep disorders [13], adopting multidisciplinary techniques and methodologies that synthesize the diverse sources of information available.

Starting with archaeological findings, physical traces of past human populations and their environments provide crucial insights into historical disease outbreaks. This includes the analysis of skeletal or mummified remains which can reveal signs of diseases, such as lesions indicating arthritis, fractures, syphilis or tuberculosis [14,15]. Additionally, extracting ancient DNA from these remains allows for the identification of specific disease biomarkers or pathogens that caused diseases in the past, confirming, for example, the presence of the bacterium *Yersinia pestis* responsible for the Black Death in medieval human remains [16,17].

Artifacts and ecological data further complement this picture by indicating the living conditions that may have influenced disease spread, such as evidence of crowding or poor sanitation [18]. Historical records also play a vital role by providing narratives and quantitative data about disease outbreaks. Chronicles and letters from the past often contain descriptions of symptoms and death tolls, as well as societal responses to these outbreaks. Medical treatises from those periods can offer insights into contemporary understandings of diseases and their treatments, reflecting the medical practices of the time. Economic and legal documents, such as records of trade and labor availability, help trace the broader societal disruptions caused by epidemics and other major diseases, and provide context for the measures societies took in response to disease outbreaks. Arts, sculptures, paintings, and other forms of cultural expression also contribute to our understanding by depicting the human experience during times of disease. These artistic works can reveal how societies perceived and coped with illness, highlighting the emotional and psychological impact of epidemics on individuals and communities. Through these diverse sources, we can piece together a more comprehensive and nuanced picture of how past societies dealt with the challenges posed by widespread disease [19,20].

Recent advancements in text mining, Natural Language Processing, and digital humanities, including Google's NGram Viewer, enable to investigate historical trends in disease incidence by analyzing the frequency of specific disease-related words in non-scholarly literature. For instance, Walker [21] assessed the frequency of scabies, a skin condition caused by *Sarcoptes scabiei mites*, in English literature from 1800 to 2019. While previous research suggested periodic cycles of 7, 15, and 30 years, employing spectral analysis, a dominant cycle of approximately 32 years could be found. This was confirmed through statistical analysis using periodograms and Fast Fourier Transform, indicating that word frequency can reflect actual disease incidence. Peaks in scabies-related word usage often correlated with significant historical events like wars, suggesting that societal disruptions may influence disease prevalence. In another study [22], Walker examined the relationship between the frequency of the word "typhus" and historical patterns of epidemic typhus, caused by *Rickettsia prowazekii* and transmitted by body lice. The analysis revealed that typhus word usage increased during periods of industrialization and major conflicts, such as World War I and World War II, and declined following public health interventions and the advent of antibiotics. The study found strong correlations between typhus and terms like "conflict" and "warfare", though less so than expected. The cyclical pattern observed suggested a cycle length of approximately 33 years, aligning closely with the findings in the scabies study. Both studies demonstrate the utility of non-traditional data sources, like Google NGram Viewer, for historical epidemiological research. The analyses relied on LOESS regression to detrend the data and spectral analysis to identify cyclical patterns. They concluded that word frequency in literature can serve as a proxy for disease incidence, offering insights especially where historical medical records are scarce. These studies highlight how historical text analysis can uncover patterns in disease incidence, correlate with significant societal events, and reflect public health interventions' impact. This approach provides a novel perspective on understanding past disease trends and the factors influencing them.

Genetic data can add a modern dimension to these analyses by helping trace the evolution and historical migration patterns: genomics can enable the reconstruction of the genomes of ancient pathogens and comparing them with those of contemporary strains. Also, studying the human genome for markers of disease resistance or susceptibility sheds light on how populations adapted

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to historical epidemics and disease outbreaks, revealing genetic traits passed down through generations. Integrating these sources involves temporal and spatial mapping to pinpoint when and where diseases appeared and how they spread geographically [23–25].

Big Epidemiology: Integrating Diverse Data

Historical records provide the context necessary to interpret archaeological and genetic data, linking disease outbreaks to social upheaval, population declines, or changes in economic systems. Genetic studies of both pathogens and human populations can reveal the co-evolutionary dynamics that have shaped the interactions between humans and diseases throughout history. This comprehensive approach enables a deeper understanding of the complex interplay between human societies and infectious diseases over millennia. By learning from the past, we can glean lessons that are crucial for managing health in today's globalized and rapidly changing world.

Such research will improve our understanding of how diseases have influenced demographic changes, migrations, and societal transformations. Another key focus is the co-evolution of pathogens and their human hosts. By utilizing genomic technologies, researchers can study changes in both pathogens and human genetics to understand susceptibility, resistance, and adaptation processes over time. This will inform strategies for managing emerging pathogens and anticipating future shifts in disease dynamics due to evolutionary changes.

The approach can also be leveraged for analyzing how environmental changes and socioeconomic factors contribute to disease emergence and re-emergence. Integrating data from climate science, urban development, and economic history will assess their roles in disease spread and management, guiding public health planning and interventions that consider long-term and global environmental and economic trends. Global health governance and disease response are also crucial. By reviewing historical and contemporary policy responses to pandemics and disease outbreaks, including institutional roles and international cooperation, the research will enhance future global responses to dseases by understanding what has worked (and what has not worked) in past global public health crises. Technological and methodological innovations in epidemiology are essential. Innovations in bioinformatics, data integration, and simulation modeling, including the latest achievements and developments in generative Artificial Intelligence, are needed to handle large-scale, multidisciplinary health data, enabling more precise and predictive epidemiological studies that can better inform public health decisions and interventions.

Lastly, the ethical, legal, and social implications of large-scale epidemiological studies and interventions must be addressed. Engaging ethicists, legal scholars, and public stakeholders in the development of frameworks that respect individual rights and promote collective health will ensure that epidemiological research and its applications are conducted responsibly and ethically.

Big Epidemiology: The Opportunities

Big Epidemiology presents significant opportunities to revolutionize our understanding and management of global health challenges. By integrating insights from diverse fields, this approach can uncover previously hidden connections between diseases and societal factors. For instance, analyzing ancient DNA alongside historical records can provide a detailed picture of how past societies responded to epidemics and disease outbreaks, offering valuable lessons for contemporary public health strategies. This comprehensive perspective enables the identification of long-term trends and patterns in disease spread and evolution, informing more effective prevention and intervention strategies.

Additionally, Big Epidemiology can drive technological and methodological innovations, such as the development of advanced data analytics tools and bioinformatics techniques. These innovations not only enhance research capabilities but also have broader applications in other scientific domains. The framework also fosters global collaboration, encouraging the sharing of data and expertise across borders, which is crucial for addressing transnational global public health issues.

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Ultimately, Big Epidemiology holds the potential to transform public health by providing a deeper, more integrated understanding of how diseases interact with human societies over time, leading to more resilient and adaptive health systems worldwide.

Big Epidemiology: The Challenges

Big Epidemiology faces numerous challenges in its ambitious goal to integrate diverse disciplines for a comprehensive understanding of disease patterns and impacts. One significant hurdle is the complexity of merging vast and varied data sources, including archaeological findings, genetic data, historical records, and environmental information. Ensuring the accuracy and reliability of these data, often fragmented and contextually diverse, is crucial. There is, indeed, considerable debate among historians about whether we will ever be able to accurately identify, from a modern biological perspective, which diseases existed in the past, which diseases were responsible for specific well-known illness episodes, and whether it is advisable to attempt retrospective modern biological diagnoses at all. This is known as the "Cunningham debate" [19], arguing against the use of retrospective diagnosis due to the incommensurability of old and new disease concepts, and emphasizing the importance of understanding the social context of past diagnoses rather than imposing modern medical perspectives.

Additionally, interpreting ancient DNA and correlating it with historical and environmental contexts demands sophisticated methodologies and technologies, which are continually evolving. The interdisciplinary nature of Big Epidemiology necessitates collaboration across fields that traditionally operate in silos, requiring effective communication and a shared framework for data integration and analysis. Moreover, ethical considerations, such as the privacy of genetic information and the potential misuse of historical data, must be carefully navigated. Addressing these challenges involves not only advancing technological and methodological innovations but also fostering an inclusive and ethical research environment. Balancing the need for comprehensive data with the respect for individual rights and historical contexts is essential for the responsible advancement of Big Epidemiology. As this field grows, it must continuously adapt to new scientific discoveries and societal needs, ensuring its relevance and impact on global public health strategies.

Big Epidemiology: The Solutions

Addressing the challenges of Big Epidemiology requires innovative solutions that foster interdisciplinary collaboration and technological advancement. To integrate diverse data sources effectively, developing standardized protocols and frameworks for data collection, storage, and analysis is crucial. Advanced bioinformatics tools and machine learning algorithms can enhance the accuracy and efficiency of interpreting complex datasets, enabling researchers to uncover patterns and correlations across different disciplines. Establishing interdisciplinary research centers and collaborative platforms can facilitate communication and knowledge sharing among experts from various fields, promoting a holistic approach to understanding disease dynamics. Ethical considerations can be managed by creating robust guidelines that protect individual privacy and ensure the responsible use of historical and genetic data. Public engagement and transparent communication are essential to build trust and address societal concerns regarding epidemiological research. Furthermore, fostering international cooperation can help address global health challenges more effectively, leveraging diverse perspectives and resources.

By combining these solutions, Big Epidemiology can overcome its inherent challenges, advancing our understanding of disease patterns and informing public health strategies on a global scale.

Recent Innovations in Epidemiology and Future Directions

Recent innovations can significantly advance Big Epidemiology, enhancing our understanding of historical and contemporary disease patterns. The integration of big data analytics and machine learning has revolutionized the processing of vast datasets from diverse sources, including historical

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records, genomic sequences, and environmental data. Innovations in genomic technologies, including next-generation sequencing, have enabled researchers to identify genetic factors in disease susceptibility and trace the evolution of pathogens through history.

Advances in geographic information systems (GIS) and spatial analysis have improved our ability to map disease spread and understand the impact of environmental changes on health. Additionally, the emerging field of genoeconomics, which studies the genetic influences on economic behavior and outcomes, offers new insights into how genetic factors may intersect with socioeconomic conditions to influence health patterns over time [26,27].

Looking forward, the future of Big Epidemiology lies in further integrating these technologies to develop predictive models that can anticipate disease outbreaks and identify at-risk populations with greater accuracy. Personalized medicine, driven by historical and genetic insights, promises to tailor interventions to individual needs, enhancing treatment efficacy. The increasing emphasis on a One Health approach, recognizing the interconnectedness of human, animal, and environmental health, will guide future research and policy in Big Epidemiology. Collaboration across disciplines and international borders will be essential to address global health challenges, ensuring that innovations in Big Epidemiology continue to enrich our understanding and management of diseases on a global scale.

Big Epidemiology: The Research Agenda and Manifesto

The research agenda and manifesto of Big Epidemiology outline a transformative vision for understanding and combating diseases through an interdisciplinary, historical lens. This ambitious framework begins by mapping the historical occurrences and societal impacts of diseases using a vast array of data sources, from archaeological findings and genetic data to historical records and environmental studies. The agenda emphasizes the importance of advanced bioinformatics and data integration tools to manage and analyze large, complex datasets. It calls for the creation of interdisciplinary research centers that promote collaboration across fields and foster innovative approaches to studying disease patterns. The manifesto advocates for ethical research practices, ensuring the privacy of genetic information and the responsible use of historical data. It also highlights the need for public engagement and transparent communication to build trust and address societal concerns. By learning from the past, Big Epidemiology aims to inform modern public health strategies, enhance global health governance, and anticipate future disease dynamics. This comprehensive approach seeks to not only understand the co-evolution of pathogens and human populations but also address the socioeconomic and environmental factors contributing to disease emergence and re-emergence. The ultimate goal is to create resilient and adaptive health systems capable of managing current and future public health challenges on a global scale.

Conclusions

Understanding and managing diseases requires a multidisciplinary approach that integrates genetics, epidemiology, public health, and clinical medicine, as well as social sciences and humanities. The concepts of disease dynamics, disease ecology, and pathocenosis emphasize the importance of considering interactions between multiple health conditions within a population. Recent advancements in genomics and evolutionary biology highlight the role of evolutionary histories and genetic variations in disease susceptibility.

Under these premises, the “Big Epidemiology” approach aims to combine historical, genetic, environmental, and societal data to address global health challenges through an integrated lens. Mapping historical disease occurrences and studying the co-evolution of pathogens and human hosts provide insights into disease dynamics, guiding future public health strategies. Technological innovations in data analytics and bioinformatics can enhance research capabilities. To integrate diverse data sources and foster interdisciplinary collaboration, standardized protocols, ethical guidelines, and international cooperation are essential. Public engagement and transparent communication build trust and ensure responsible data use. Big Epidemiology offers significant

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opportunities to revolutionize our understanding and management of global health issues, creating resilient and adaptive health systems to address current and future public health challenges globally.

In conclusions, through this agenda, Big Epidemiology seeks to profoundly impact how we understand, prevent, and respond to diseases on a global scale, leveraging a historical perspective to enrich and guide modern scientific inquiry and public health strategies.

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