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# Emerging infectious disease prevention: Where should we invest our resources and efforts?

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ABSTRACT

Strategies focused on the prevention of emerging infectious disease outbreaks are currently in the spotlight of discussions among researchers committed to infectious disease control. In this mini-review, we provided a brief update on this discussion and characterized the three main targets for investments in emerging infectious disease prevention: animals, human sentinels for spillover events, and the general human population. Furthermore, the pros and cons of each target are highlighted. Despite the particularities of the proposed targets, each of them can fill different gaps in the surveillance of infectious diseases. When all three targets are focused on together, they create a powerful strategy of emerging infectious disease prevention.



**Contents**



## Introduction

Although it seems paradoxical considering the general advances in health sciences, emerging infectious diseases (EIDs) have become more frequent in recent decades [1]. Environmental changes due to human activity, increased international mobility, poor public health systems, and microbial adaptations are some of the main drivers of this problem [2,3]. To efficiently combat EIDs, scientific and governmental communities use different approaches focused on the prediction, rapid detection, and surveillance of pathogens with the potential to cause outbreaks, epidemics, and even pandemics. However, the high pathogen diversity in nature makes the prediction of which pathogens have a real potential of causing diseases in humans a large challenge. Considering this fact, researchers committed to EID prevention frequently need to make complex decisions about the best aspect they should focus their actions and financial resources on, which are often highly limited, especially in low-income countries.

## Targets for investments in emerging infectious disease prevention

The discovery of new potential human pathogens is a useful strategy for EID prevention [4]. However, given the high cost and uncertainty about its effectiveness, this strategy has been highly criticized [5]. Considering that it is expensive to test ani-

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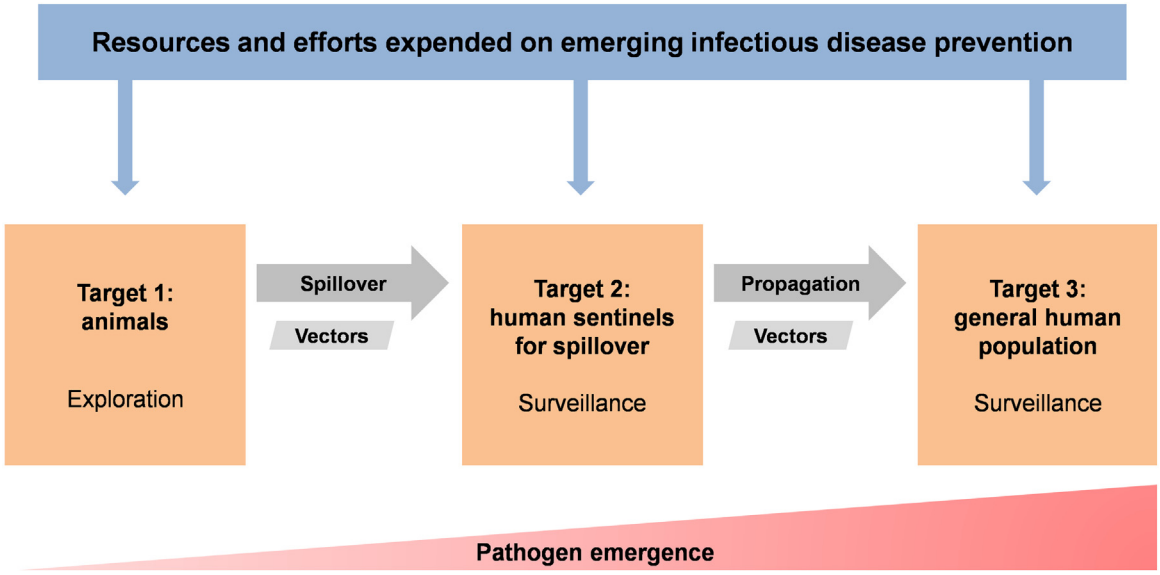


**Fig. 1.** Targets for investments in EID prevention.

mal populations for previously unrecognized pathogens, testing for pathogens that have already crossed the barrier between animals and humans (spillover) [6] could be a more cost-efficient use of limited resources. Additionally, the early detection of EIDs based on effective surveillance of pathogens circulating in human populations would be easier than the attempt to predict "when and where" EID events will occur [5,7]. In our opinion, efforts expended in each of the strategies mentioned above promote different impacts on EID prevention. To explain and discuss such strategies, it is necessary to help researchers organize and optimize their actions to obtain the best return from the scarce resources available for this purpose. Most EIDs are zoonoses [1], and considering the basic steps of zoonotic disease emergence [8], we summarized here the major investment targets for EID prevention (Fig. 1). EID drivers and pathogen characteristics that facilitate spillover are not included in our discussion. In brief, a simple question should be asked: who should be tested/evaluated to provide a better understanding of the actual prevalence of EIDs?

- *Target 1: animals.* The investigation of already known or even unknown microorganisms hosted in animals would help in the identification and tracking of pathogens that, at some point, may cause human diseases. However, most of the pathogens circulating in wild animals will never cause human diseases or pandemics [6,9]. In addition, this strategy can be very costly and has little immediate practical applicability [5]. However, this approach is valuable in outbreak situations. For example, the development of a vaccine or therapeutic strategies for new human diseases can be accelerated if the genome sequences or other biological aspects of the pathogen are already available before the outbreak event [3,4]. Of note, focusing investigations on key animals (e.g., companion animals, livestock, and select wild animals, such as bats) may be more advantageous since they are in close contact with humans and can act as spillover intermediates [8,10]. In the context of EID prevention, targeting broad-spectrum pathogen detection in animals is an exploratory-type strategy.

- *Target 2: human sentinels for spillover events.* Zoonotic pathogens found in human biological samples represent a small number of microorganisms that have successfully moved from animals to humans [6]. Individuals in close and frequent contact with wild animals and livestock (e.g., hunters, farmers, and veterinarians) can act as human sentinels of recent spillover events [7]. Scientists who work with human sentinels direct their efforts to detect pathogens that already infect humans but have little epidemiological importance. Once a new human pathogen is detected, response actions such as the elucidation of its medical importance and surveillance intensification can be taken. However, if the spillover is not rapidly identified or if adequate control measures are not taken, the pathogen will have the opportunity to spread among the human population.

- *Target 3: general human population.* Screenings performed in blood donor samples or samples from other specific groups may be useful to detect the circulation of emerging pathogens at a population level. This action requires an adequate laboratory and technical structure. In this context, it is important to emphasize that low-income countries will require substantial efforts concerning investments to build laboratories and train staff to address the diagnosis of infectious diseases [11]. The strategies mentioned in the previous topics can help to determine which pathogens should be included in such screenings. A fundamental feature of pathogens that cause epidemics or pandemics is the ability to move between humans through direct human-to-human transmission [6,9]. Once observed, this specific transmission pattern should not be neglected. However, various microorganisms circulating in humans are neither pathogenic nor epidemiologically important. Therefore, microbial screening in the general population can be very useful for EID prevention but can sometimes trigger false alarms.

The prevention strategies summarized in targets 2 and 3 (targeting human sentinels or the general human population) present a surveillance-type characteristic. In addition to the three targets mentioned here, vectors cannot be overlooked in EID prevention since they play important roles in pathogen transmission from animals to humans as well as in sustaining outbreaks. For example, mosquitoes sustain the endemic, epidemic, and sylvatic cycles of Zika virus [12] and Dengue virus [13]. Additionally, ticks are responsible for the transmission of various pathogens between animals and humans [14]. For these reasons, the surveillance of pathogens in vectors must also be encouraged and expanded.

## Pivotal considerations and perspectives: Strengthen the basics and invest in new technologies

The transmission of pathogens between humans is divided into direct and indirect modes. The direct transmission modes are

vertical (e.g., transplacental or during vaginal birth), sexual (e.g., genital-genital or oral-genital), nonsexual direct contact (e.g., kissing or touching), and airborne (e.g., respiratory tract-respiratory tract). The indirect transmission modes are environmental (e.g., infected water-oral or contaminated food-oral), fomites (e.g., needle-blood or doorknob-hand), and vector-borne (e.g., cutaneous penetration or vector fecal deposition) [15]. Direct human-to-human transmission should receive special attention in EID prevention strategies since, as mentioned before, this is the mode of transmission that sustains epidemics [6,9]. However, indirect modes of transmission are crucial in some cases. For example, the role of mosquitoes in epidemics caused by arboviruses is extremely relevant and cannot be neglected [12,13].

Many advances have already been made in developing pipelines and strategies to prevent and mitigate outbreaks. For example, once the etiologic agent of an infectious disease is detected, conduits to stop the transmission chain can be easily established based on the knowledge of the transmission modes responsible for the pathogen transmission. However, these actions often run counter to factors such as the lack of basic sanitation and low education levels of the population affected by a disease outbreak, factors that hamper the adequate establishment of strategies to mitigate infectious diseases. Thus, EID prevention is dependent on the strengthening of basic social and environmental factors, such as population access to education and health services, as well as environmental preservation. In other words, it is necessary to prioritize the One Health approach, in which human, animal, and environmental factors are considered together in EID prevention and mitigation strategies [16–18].

In addition to focusing on basic strategies, investing in new diagnostic technologies and tools of pathogen detection is crucial. Classically, epidemiological surveillance in human populations requires the selection of which pathogens will be monitored. For this task, it is necessary to know which pathogens circulate in a given population and which pathogens have relevance to be monitored at a population level and to have cost-effective diagnostic tools to perform the surveillance quickly and effectively. New diagnostic technologies are changing this scenario and reducing these problems, such as DNA microarray platforms capable of detecting several pathogen species in a single biological sample [19–21]. Additionally, portable sequencers [22,23] and CRISPR/Cas-based methods [24–26] are important new tools for pathogen diagnostics in the field. However, methods for pathogen screening or rapid and precise microbial detection are generally expensive, and there is still a need to develop cost-effective tools to allow their implementation even in low-income countries. Although the tools mentioned above are not yet part of most laboratories and are still not available for all teams responsible for epidemiological surveillance, they exemplify how investing in the development of new diagnostic technologies can positively impact surveillance strategies.

In the case of strategies focused on pathogen exploration, metagenomic strategies allow the identification of which groups of pathogens are present in environmental, animal, or clinical samples, in addition to knowing the abundance of pathogen groups found in the sample. In addition, the obtained DNA sequences can be used for phylogenetic and phylogeographic analyses, allowing for the understanding of evolutionary aspects of the pathogens, the reconstruction of transmission chains, and even the estimation of the probable starting date of an outbreak [27–29]. Metagenomics tools are constantly being refined [30], and their use in strategies for pathogen exploration is increasing. In addition to discovering new pathogens circulating in humans, when metagenomic studies are performed using samples from vectors or wildlife [31,32], they allow the discovery of new pathogens with the potential of experiencing spillover. However, it is important to remember that spillover is a complex process [6], and after a new virus is identified in wildlife, it is necessary to evaluate very carefully whether it represents a threat to human health [33].

## Concluding remarks

In conclusion, human and monetary investments focused on animals, humans, and vectors meet different demands and support the elucidation of different questions in the EID context. Taken together, they are profoundly complementary and give rise to powerful strategies for EID prevention. In essence, all the strategies discussed here are based on surveillance and early detection of human health threats. Researchers and governmental agencies should choose the appropriate targets for their future investments based on the pros and cons of each of them and take into account the available resources and the most urgent needs of their communities and countries or the global scenario. Answering the question mentioned before, we suggest the following approaches: animals and human sentinels for spillover events could be targeted in research initiatives, in which a large number of resources are available. Additionally, the general human population should be evaluated as part of public health programs. In the best possible scenario, the three groups should be targeted together.

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## Competing interests

None declared.

## Ethical approval

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## References

[1] Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, et al. Global trends in emerging infectious diseases. Nature 2008;451:990–3, http://dx.doi.org/10.1038/nature06536.
[2] Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis 1995;1:7–15, http://dx.doi.org/10.3201/eid0101.950102.
[3] Howard CR, Fletcher NF. Emerging virus diseases: can we ever expect the unexpected? Emerg Microbes Infect 2012;1:e46, http://dx.doi.org/10.1038/emi.2012.47.
[4] Carroll D, Daszak P, Wolfe ND, Gao GF, Morel CM, Morzaria S, et al. The global virome project. Science 2018;359:872–4, http://dx.doi.org/10.1126/science.aap7463.
[5] Holmes EC, Rambaut A, Andersen KG. Pandemics: spend on surveillance, not prediction. Nature 2018;558:180–2, http://dx.doi.org/10.1038/d41586-018-05373-w.
[6] Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, et al. Pathways to zoonotic spillover. Nat Rev Microbiol 2017;15:502–10, http://dx.doi.org/10.1038/nrmicro.2017.45.
[7] Cleaveland S, Haydon DT, Taylor L. Overviews of pathogen emergence: which pathogens emerge, when and why? Curr Top Microbiol Immunol 2007;315:85–111.
[8] Morse SS, Mazet JA, Woolhouse M, Parrish CR, Carroll D, Karesh WB, et al. Prediction and prevention of the next pandemic zoonosis. Lancet 2012;380:1956–65, http://dx.doi.org/10.1016/S0140-6736(12)61684-5.
[9] Lloyd-Smith JO. Infectious diseases: predictions of virus spillover across species. Nature 2017;546:603–4, http://dx.doi.org/10.1038/nature23088.
[10] Bean AG, Baker ML, Stewart CR, Cowled C, Deffrasnes C, Wang LF, et al. Studying immunity to zoonotic diseases in the natural host — keeping it real. Nat Rev Immunol 2013;13:851–61, http://dx.doi.org/10.1038/nri3551.
[11] Ahmed SS, Alp E, Ulu-Kilic A, Doganay M. Establishing molecular microbiology facilities in developing countries. J Infect Public Health 2015;8:513–25, http://dx.doi.org/10.1016/j.jiph.2015.04.029.

[12] Lessler J, Chaisson LH, Kucirka LM, Bi Q, Grantz K, Salje H, et al. Assessing the global threat from Zika virus. Science 2016;353:aaf8160, http://dx.doi.org/10.1126/science.aaf8160.
[13] Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a dengue virus vaccine. Nat Rev Microbiol 2007;5:518–28, http://dx.doi.org/10.1038/nrmicro1690.
[14] Vayssier-Taussat M, Cosson JF, Degeilh B, Eloit M, Fontanet A, Moutailler S, et al. How a multidisciplinary 'one Health' approach can combat the tick-borne pathogen threat in Europe. Future Microbiol 2015;10:809–18, http://dx.doi.org/10.2217/fmb.15.15.
[15] Antonovics J, Wilson AJ, Forbes MR, Hauffe HC, Kallio ER, Leggett HC, et al. The evolution of transmission mode. Philos Trans R Soc Lond B Biol Sci 2017;372, http://dx.doi.org/10.1098/rstb.2016.0083.
[16] Calistri P, Iannetti S, Danzetta ML, Narcisi V, Cito F, Sabatino DD, et al. The components of 'one World — one Health' approach. Transbound Emerg Dis 2013;60(Suppl. 2):4–13, http://dx.doi.org/10.1111/tbed.12145.
[17] Jones BA, Betson M, Pfeiffer DU. Eco-social processes influencing infectious disease emergence and spread. Parasitology 2017;144:26–36, http://dx.doi.org/10.1017/S0031182016001414.
[18] Ellwanger JH, Chies JAB. Zoonotic spillover and emerging viral diseases — time to intensify zoonoses surveillance in Brazil. Braz J Infect Dis 2018;22:76–8, http://dx.doi.org/10.1016/j.bjid.2017.11.003.
[19] Wang D, Coscoy L, Zylberberg M, Avila PC, Boushey HA, Ganem D, et al. Microarray-based detection and genotyping of viral pathogens. Proc Natl Acad Sci U S A 2002;99:15687–92, http://dx.doi.org/10.1073/pnas.242579699.
[20] Khan MJ, Trabuco AC, Alfonso HL, Figueiredo ML, Batista WC, Badra SJ, et al. DNA microarray platform for detection and surveillance of viruses transmitted by small mammals and arthropods. PLoS Negl Trop Dis 2016;10:e0005017, http://dx.doi.org/10.1371/journal.pntd.0005017.
[21] Ellwanger JH, Kaminski VL, Chies JAB. How to detect new viral outbreaks or epidemics? We need to survey the circulation of viruses in humans and other animals using fast, sensible, cheap, and broad-spectrum methodologies. Braz J Infect Dis 2017;21(2):211–2, http://dx.doi.org/10.1016/j.bjid.2016.12.001.
[22] Yamagishi J, Runtuwene LR, Hayashida K, Mongan AE, Thi LAN, Thuy LN, et al. Serotyping dengue virus with isothermal amplification and a portable sequencer. Sci Rep 2017;7(1):3510, http://dx.doi.org/10.1038/s41598-017-03734-5.
[23] Ashikawa S, Tarumoto N, Imai K, Sakai J, Kodana M, Kawamura T, et al. Rapid identification of pathogens from positive blood culture bottles with the MinION nanopore sequencer. J Med Microbiol 2018;67(11):1589–95, http://dx.doi.org/10.1099/jmm.0.000855.
[24] Gootenberg JS, Abudayyeh OO, Lee JW, Essletzbichler P, Dy AJ, Joung J, et al. Nucleic acid detection with CRISPR-Cas13a/C2c2. Science 2017;356(6336):438–42, http://dx.doi.org/10.1126/science.aam9321.
[25] Chen JS, Ma E, Harrington LB, Da Costa M, Tian X, Palefsky JM, et al. CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity. Science 2018;360(6387):436–9, http://dx.doi.org/10.1126/science.aar6245.
[26] Myhrvold C, Freije CA, Gootenberg JS, Abudayyeh OO, Metsky HC, Durbin AF, et al. Field-deployable viral diagnostics using CRISPR-Cas13. Science 2018;360(6387):444–8, http://dx.doi.org/10.1126/science.aas8836.
[27] Firth C, Lipkin WI. The genomics of emerging pathogens. Annu Rev Genomics Hum Genet 2013;14:281–300, http://dx.doi.org/10.1146/annurev-genom-091212-153446.
[28] Wohl S, Schaffner SF, Sabeti PC. Genomic analysis of viral outbreaks. Annu Rev Virol 2016;3(1):173–95, http://dx.doi.org/10.1146/annurev-virology-110615-035747.
[29] Gardy JL, Loman NJ. Towards a genomics-informed, real-time, global pathogen surveillance system. Nat Rev Genet 2018;19:9–20, http://dx.doi.org/10.1038/nrg.2017.88.
[30] Metsky HC, Siddle KJ, Gladden-Young A, Qu J, Yang DK, Brehio P, et al. Capturing sequence diversity in metagenomes with comprehensive and scalable probe design. Nat Biotechnol 2019;37:160–8, http://dx.doi.org/10.1038/s41587-018-0006-x.
[31] Razzauti M, Galan M, Bernard M, Maman S, Klopp C, Charbonnel N, et al. A comparison between transcriptome sequencing and 16S metagenomics for detection of bacterial pathogens in wildlife. PLoS Negl Trop Dis 2015;9:e0003929, http://dx.doi.org/10.1371/journal.pntd.0003929.
[32] Geldenhuys M, Mortlock M, Weyer J, Bezuidt O, Seamark ECJ, Kearney T, et al. A metagenomic viral discovery approach identifies potential zoonotic and novel mammalian viruses in *Neoromicia* bats within South Africa. PLoS One 2018;13:e0194527, http://dx.doi.org/10.1371/journal.pone.0194527.
[33] Temmam S, Davoust B, Berenger JM, Raoult D, Desnues C. Viral metagenomics on animals as a tool for the detection of zoonoses prior to human infection? Int J Mol Sci 2014;15:10377–97, http://dx.doi.org/10.3390/ijms150610377.