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Commentary

The reemergence of measles and the urgent need for uninterrupted genetic surveillance and vaccination

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Background

In an era marked by unprecedented global health challenges, measles virus (MeV) reemerges as a significant threat to public health, despite being one of the most preventable diseases through vaccination. Caused by an enveloped, single-stranded negative-sense RNA virus of the genus *Morbillivirus*, measles is not only highly contagious but also present in various strains, with at least 20 different genotypes identified across the globe [1]. Despite this genetic diversity, there exists only one serotype of MeV, making its widespread impact particularly daunting [1]. An infected individual is likely to transmit the virus to over 90% of unprotected close contacts, underscoring the disease's capability to trigger extensive outbreaks [2]. Diagnosis of MeV is typically made by detecting the virus in clinical specimens using laboratory tests such as the reverse transcription polymerase chain reaction (RT-PCR) or serological assays [3]. Recently, the integration of this methodology with whole genome sequencing has facilitated the identification of a new MeV variant, highlighting mutations that might influence transmission dynamics and immune responses [4]. This situation further underscores the critical role of epidemiological surveillance, not only for the continuous monitoring of the spread of measles but also for the early detection of its variants. In this context, the introduction of innovative surveillance methods, such as wastewater analysis, becomes crucial. This method has shown efficacy in tracking the presence of SARS-CoV-2 during the COVID-19 pandemic [5,6] and offers a promising approach for surveilling other infectious diseases, including measles. For example, research conducted in the Netherlands used wastewater monitoring to track poliovirus and measles, demonstrating its feasibility as an early detection tool for these viruses [7].

The integration of advanced detection techniques, such as wastewater analysis, into global epidemiological surveillance could revolutionize our ability to respond quickly to public health emergencies. This not only enhances our capacity for rapid and targeted intervention but also sets a new standard in public health, aiming for proactive rather than reactive protection of at-risk communities.

Genetic variants of MeV

MeV possesses a genome consisting of single-stranded negative-sense RNA, which encodes for six structural and two nonstructural proteins [8]. Among these proteins, MeV has two envelope transmembrane glycoproteins: hemagglutinin and fusion. Hemagglutinin binds to cellular receptors, while the fusion protein is initially produced in a metastable state and facilitates the fusion of the viral envelope with the target cell membrane [9]. Working

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together, hemagglutinin and fusion form the fusion complex, which facilitates the viral entry into the host cells. In addition, the ribonucleo-(N), phospho-(P), and large proteins constitute the ribonucleoprotein complex, which is crucial for protecting genomic RNA and facilitating its replication and transcription. The M protein plays a role in coordinating the assembly of viral particles and initiating their budding at the cell membrane. Two nonstructural proteins, V and C, transcribed from the *P* gene, have roles that are less well understood but are likely to function as virulence factors within the host cell [10].

The genetic variability of the measles variant can decrease the sensitivity of diagnostic tests due to mismatches between primers or probes and the template [4]. In the 1990s, measles continued to be a highly contagious disease caused by an RNA virus of the genus *Morbillivirus*, characterized by a single serotype. Although genotype A, isolated in 1954, serves as the reference strain, it is one among multiple genotypes belonging to this serotype [11,12]. Thanks to vaccination, there was a significant reduction in the incidence of measles worldwide. The WHO recognizes eight clades (A–H) of the MeV, which are further subdivided into 24 genotypes: A, B1, B2, B3, C1, C2, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, E, F, G1, G2, G3, H1, and H2 [13]. As of today, three out of the 24 recognized genotypes of the MeV are accountable for global outbreaks [14]. The H1 has been the prevalent lineage in China for several years [15] and was detected for the last time in 2019 [16]. The B3, primarily found in African nations where it originated, is now widespread globally, and the D8, which emerged in Asia during the 1980s, is currently spread worldwide [17]. Genotypes D8 and B3 have been responsible for outbreaks occurring over the last years across Europe, Asia, and North America [18]. In general, the D8 variant of measles is a known genotype of the MeV, which may present mutations that result in a slight loss of sensitivity to some molecular tests. However, the vaccine in use continues to be effective against this variant.

Among the most recent developments, in 2023 the genetic variant 8248 raised some concerns. It was linked to the lineage MVs/Patan.IND/16.19, and, although originated in Tajikistan, became dominant in Russia, where the number of measles cases associated predominantly with the genetic variant 8248 notably increased during 2022–2023 [19]. The persistence of this variant in Russia is primarily sustained through the continuous importation of measles cases from Tajikistan. Furthermore, isolated measles cases connected with this variant were reported sporadically in Kazakhstan, the Czech Republic, the United Kingdom, the United States [19], Russia, Saudi Arabia, and Italy [4] in 2023. It was characterized by three synonymous mutations resulting from the substitution of a Thymine with a Cytosine in the N-450 region in positions 75, 78, and 81 (Fig. 1).

The last new measles D8 variant has been labelled variant 8491 [20]. This new variant is quite different from the previous variant 8248, with a mean genetic distance of 0.035 (±0.001) estimated in the N-450 region, which is recommended by the WHO for diagnostic genotyping of MeV [3]. See Fig. 1 for polymorphic sites in the N-450 region of 8248 and 8491 genetic variants.

Sequences were analysed using WebLogo (https://weblogo.berkeley.edu/logo.cgi), illustrating levels of conservation and variation within this critical region of the MeV genome.

It is important to highlight that the emergence of new genetic variants poses unique challenges that can affect the effectiveness of vaccination. This genetic variability can impact various aspects of

Fig. 1. Graphical representation of sequence alignment of the N-450 region of 8248 and 8491 genetic variants.

the disease, including the host's immune response and susceptibility to infection [21]. Certain mutations in the virus have been observed to diminish the effectiveness of the immune response induced by vaccination [21], potentially increasing susceptibility to infection among vaccinated individuals and contributing to measles outbreaks even in communities with high vaccination coverage. Moreover, the genetic variability of the virus can impact the long-term effectiveness of vaccination, as continuously evolving viral strains may necessitate periodic updates to vaccines to ensure adequate protection against the disease [22]. Hence, ongoing genetic surveillance of the MeV is essential, along with the development of adaptive vaccination strategies. Addressing these challenges requires maintaining high vaccination coverage rates and implementing targeted and effective vaccination programmes. In addition, coordinated global efforts are necessary to monitor and respond to the genetic variability of the MeV, including research and development of new vaccines and vaccination strategies [22].

Discussion

The resurgence of measles, a highly preventable disease, amidst the backdrop of the COVID-19 pandemic, underscores the vital importance of vaccination in public health strategies [23]. Vaccination not only limits the spread of measles but also plays a crucial role in preventing its reemergence [23]. The staggering potential for an infected individual to transmit the virus to over 90% of unprotected close contacts highlights the necessity of maintaining high vaccination coverage rates. As such, enhancing vaccine accessibility and addressing vaccine hesitancy are imperative to forestall the resurgence of measles and to safeguard community health. Moreover, the innovative use of wastewater surveillance has emerged as a powerful tool in the epidemiological toolkit [24,25], offering a promising approach for early detection and surveillance of infectious diseases, including SARS-CoV-2 [26].

The innovative use of wastewater surveillance, as described in the study on the detection of MeV D8 genotype in Brussels wastewater, is a significant example of how such methodology can be crucial in public health strategies [27]. This technique made it possible to identify the presence of the virus in an area where cases had not been fully reported, thus suggesting more extensive transmission of the virus than detected through traditional clinical surveillance. Confirmation of the D8 genotype, corresponding to strains circulating in Europe, was possible through the use of advanced molecular techniques, such as real-time RT-PCR and nested PCR, which improved the accuracy of virus detection and genotyping from environmental samples. The importance of these findings is two-fold: on the one hand, it provides valuable confirmation of virus circulation; on the contrary, it underscores the need for standardized [28] testing methods to develop a comprehensive understanding of the spread of infectious diseases and to formulate coordinated intervention strategies.

By integrating wastewater surveillance into routine public health practices, we can enhance our ability to monitor and respond to infectious disease threats more effectively. Future interventions should prioritize the expansion of vaccination programmes, the development of public health campaigns to combat vaccine hesitancy, and the integration of advanced surveillance methods like wastewater analysis into epidemic preparedness strategies. These actions will collectively strengthen our resilience against measles and other infectious diseases, contributing to a safer, healthier future.

The concerted efforts to enhance vaccine uptake, coupled with the strategic use of wastewater surveillance, are essential in the fight against the reemergence of measles. These strategies not only highlight innovation in public health surveillance but also emphasize the critical role of vaccination in disease prevention. The insights gleaned from the COVID-19 pandemic serve as a stark reminder of the importance of global health vigilance and the need for continued investment in vaccination and surveillance technologies. Together, these measures represent a comprehensive approach to managing public health threats, ultimately leading to the preservation of global health security and the well-being of communities worldwide.

Authors contributions

F.B. participated in conceptualization, Investigation, Formal analysis, and writing (original draft preparation, review, and editing). M.G. participated in writing (original draft preparation, review, and editing). C.R. participated in writing (original draft preparation, review, and editing). A.C. participated in writing (original draft preparation, review, and editing). D.S. participated in writing (original draft preparation, review, and editing). M.C. participated in conceptualization, Investigation, Validation, and writing (original draft preparation, review, and editing). F.S. participated in conceptualization, Data curation, Investigation, Formal analysis, Visualization, and writing (original draft preparation, review, and editing). All authors have read and agreed to the published version of the manuscript.

Transparency declaration

Potential conflict of interest

The authors have nothing to disclose.

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