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Beyond the Surface: An In-Depth Look at Tomato Flu

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Abstract: While fighting the coronavirus disease 2019 (COVID-19) and monkeypox, a new viral strain known as tomato flu, or tomato fever, was discovered in the Indian subcontinent during the third phase of the severe acute respiratory syndrome coronavirus 2. This strain has been causing life-threatening issues in some Indian states, including Kerala and Tamil Nadu. As of right now, there are more than 82 confirmed instances, and the virial infection is starting to spread to other parts of India. It may be connected to hand, foot, and mouth disease (HFMD) and is thought to be caused by the enterovirus Coxsackievirus A-6.

This article contains comprehensive information about the causal virion, including its anatomy, life cycle, prevention, and treatment options. The specific details undoubtedly aid researchers in comprehending the life cycle of the causative agent, which in turn aids in the development of diverse enzyme inhibitors and the creation of novel antiviral agents. This page will assist the neighbourhood chemist in educating the public about the causes, treatments, and avoidance strategies for tomato flu.

Keywords: Tomato flu, Monkeypox, Hand-foot-mouth disease, Picornaviridae, Coxsackievirus A-6

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Introduction

Kerala, India is where the rare tomato flu illness was initially identified on May 6, 2022. It is believed to be caused by Coxsackievirus A-6, one of the Enterovirus group, and it may be related to hand, foot, and mouth disease (HFMD). The painful red blisters (Fig. 1) that resemble tomatoes that break out are what give the illness its name (Chavda *et al.*, 2023). These blisters gradually develop larger and resemble the blisters that persons with monkeypox have (Table 1) (Zee News, 2022). By July 26, 2022, 82 children from the Kollam district of Kerala had become infected with this virus, as reported in The Lancet Respiratory Medicine Journal (Zee

Table 1: Difference between Monkey pox, Tomato flu and COVID 19 (Davis. 2022)

Topic	Monkey Pox	Tomato Flu	COVID 19
Etiological Agent	Monkeypox virus (Orthomyxovirus)	Coxsackievirus A-6, A-16	SARS-CoV-2 virus
Mode of transmission	• Animal to human: zoonotic, • Human to human: respiratory secretions and droplets	• Direct contact, • Lack of hygiene	• Respiratory droplet transmission from an infected person, • airborne transmission, • direct contact with infected people and indirect contact with surfaces used by the infected person.
Symptoms	• Red painful flat bumps (Phases: macules, papules, vesicles) • fever, • swollen lymph nodes, • muscle aches, • headache, • respiratory symptoms	• Red painful fluid-filled blisters (like tomato), • fever, • joint pain and swelling, • body ache, • fatigue,	• Fever or chills, • Cough, • Shortness of breath or difficulty breathing, • fatigue, • muscle or body aches, headache, • sore throat, • loss of taste
Incubation period	3–17 days	1 week or 4-5 days	14 days
Response to human being	Children are at high risk but also adults can get.	Mainly effect the offsprings under the age of 5.	All ages of people are getting the disease.
Medication	Tecovirimat (TPOXX)	Dengue or Chikungunya medications are effective.	There are few FDA-approved oxygen medications
Complications	severe bacterial infection from skin lesions, mpox affecting the brain (encephalitis), heart (myocarditis) or lungs (pneumonia), and eye problems	Non-life threatening till now	Blood clotting has occurred in the brain, lungs, heart, legs, arteries, veins, and can be life threatening

News, 2022).

In addition, a few cases from three other states Tamil Nadu, Haryana, and Odisha have been reported (Mukherjee *et al*., 2022). It has been reported that youngsters especially those under five and immuno-compromised adults, are the virus's target demographic. It is thought that the main way the virus spreads is through close contact, especially touching contaminated surfaces (Carmona *et al*., 2022). Tomato flu shares symptoms with several other viral illnesses, such as chikungunya and the recently discovered coronavirus disease 2019 (COVID-19). Among these symptoms include painful blisters, fever, myalgia, joint swelling, and dehydration. Thus, before making a final diagnosis, several molecular and serological tests are run to rule out other illnesses (Sanjay *et al*., 2022). Following diagnosis, patients receive bed rest, symptomatic therapy, and are kept in isolation for 5-7 days

Fig. 1: Blisters of the tomato flu affected patient (A- affected hand, B-affcetd face and body, C- afftected foot, D- affected mouth).

(Page, 2022). They are also instructed to maintain adequate hydration. The vast majority of instances resolve on their own and do not constitute a substantial risk to health, despite the fact that there is no known cure for the illness. Certain adverse effects, like encephalitis and muscle paralysis, are rare (Biswas *et al*., 2022).

Because of the symptoms, which include tiny grape-like blisters that might resemble tomatoes in size and colour, the virus is known as the "tomato virus." According to reports, the ailment has spread to other parts of India and there are presently over 80 cases. Regarding the risks to the public, the tomato flu is very contagious and can be passed from person to person by intimate contact, including using nappies, touching dirty surfaces, or putting objects in mouths (Feder *et al*., 2014). Parents are advised that children with HFMD should be kept out of school or nursery for five days following the onset of symptoms, as it is very contagious and can be transmitted by faeces and the fluid in the spots. According to recent findings, tomato fever, often known as tomato flu, is actually a manifestation of hand, foot, and mouth disease (HFMD), a juvenile ailment that frequently causes a feverish rash due to Coxsackie viruses. The past several years have also seen a number of publications highlighting the various ways that HFMD has been caused by Coxsackie virus infections (Tang *et al*., 2022). Extensive literature survey revealed that very few information exists in various blogs, newspaper, websites, published review article. The updated and intensive information was not found in any of the reported article. In the present article the extensive information has been included focusing on the causative virion, its anatomy and its life cycle. The particular information definitely helps the research scientist to understand the exact life cycle of the causative agent, which further help to develop the various enzyme inhibitors and design of new antiviral agent. This article will be helping the community pharmacist to explain the reason, medication, prevention of the tomato flu to the community.

Current Indian scenario to alleviate Tomato flu

The tomato flu outbreak in India has garnered international notice in recent days. There are cases in four countries, and both domestic and international health organisations are concerned

about how quickly this outbreak is spreading (Sudhakar, 2022). Even though tomato flu has been a problem in India for about 20 years, the country has seen more cases recently than usual. Although the precise reason for the rise in cases is unknown, many have linked it to the COVID-19 pandemic's aftermath and India's reopening of schools. Indian health officials have taken the required steps to contain the outbreak, even though the World Health Organisation (WHO) has not taken a global stand on the matter (Uwishema *et al*., 2022). In order to guarantee a sufficient reaction to the outbreak, the Indian health authorities have suggested expeditious testing and boosted health surveillance. As the COVID-19 pandemic has demonstrated, prompt response is essential to reducing the effects of endemic disease outbreaks (Sudhakar, 2022). The majority of infected individuals are treated symptomatically because there are no medications or vaccinations available to treat tomato flu (Sudhakar, 2022). Isolating suspected patients for 5-7 days after the onset of symptoms is the most efficient strategy to stop the infection from spreading (Uwishema *et al*., 2022).

Symptoms

Although health officials are currently looking into instances, some symptoms of the tomato flu that are being reported include Primarily tomato-like blisters, Elevated body's temperature, Skin rashes, joint swelling, exhaustion, cramps, Aches in the body. Other symptoms include skin irritation, runny nose, coughing, nausea, vomiting, and sneezing (Symptoms, 2022).

Etiology of tomato flu

The cause of this disease is unknown. The health officials are still investigating the tomato flu disease. Tomato flu caused by a virus that may be coxsackievirus A16, an RNA virus belongs to the family Picornaviridae responsible for Hand, Foot, and Mouth Disease (usually affects children below 9 and those who have weak immune systems). The illness was given its name due to the widespread appearance of painful, red blister all over the body that eventually resembled tomatoes in shape (Cox *et al*., 2017). Infectious disease is uncommon and self-limiting. Although it does not now threaten human life, careful management is necessary to prevent it from spreading. Enterovirus A71 (EV-A71) and Coxsackievirus A16 (CV-A16) are the two primary viruses linked to HFMD. EV-A71 is the predominant strain that is linked to severe cases and mortality.Infants and young children are more vulnerable to the health risks associated with EV-A71 infections (Ren *et al*., 2020) According to a study done in Asian nations where HFMD is more prevalent, HFMD causes 96,900 disability-adjusted life years (DALYs) per year. Years of life lost were the primary cause of most of these DALYs. When an infection is caused by EV-A71, serious neurological consequences almost always result; however, CV-A16 infections are uncommon. Predicted on the theory that this could be because EV-A71 more readily infects neural cells than CV-A16 (Yogarajah *et al*., 2017; Koh *et al*., 2018).

Anatomy of Coxsackievirus A16

Coxsackievirus A16 (CV-A16) (Fig. 2) is a primary etiologic factor for hypotrophic foot disease. It belongs to the Enterovirus genus within the Picornaviridae family, specifically the Human Enterovirus A (HEV-A) species. The single-stranded, positive sense, polyadenylated RNA virus known as CV-A16 has an icosahedral symmetry structure and is about 7400 bases in length. A member of the Picornaviridae family, Coxsackievirus A16 is the main cause of hand, foot, and mouth disease, a condition that mainly affects children. As of right now, there are no antiviral medications or vaccines to treat this virus (Selvaraj *et al*., 2022) A non-structural protein called enterovirus 2A protease possesses the ability to both cleave the eukaryotic translation initiation factor and itself. The coxsackievirus A16 2A protease's crystal structure research revealed that the structure is open, allowing for substrate binding, cleavage activity, and accessibility to the active site. The

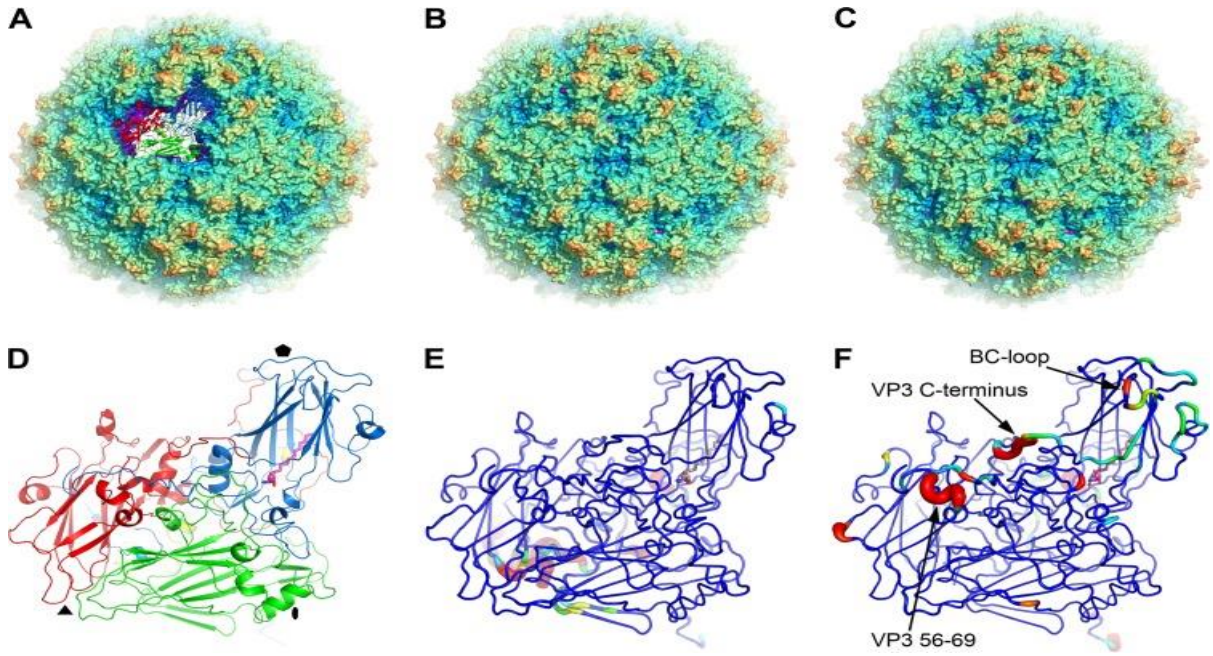

Fig. 2: Structures A= Radius-colored surface mature CVA16 (Radius-colored surface), B= Empty CVA16,C= Mature EV71 particles. respectively, cut away in panel A to highlight an individual protomer with proteins color coded as follows: VP1, blue; VP2, green; VP3, red; and VP4, yellow. D=An enlarged protomer structure of the mature CVA16 as shown in figure A. The bound pocket factor in VP1 is drawn as magenta sticks (E and F). Comparisons of the mature CVA16 protomer with those of empty CVA16 (E) and mature EV71 (F) (Garmaroudi *et al*., 2015; Wald, 2009).

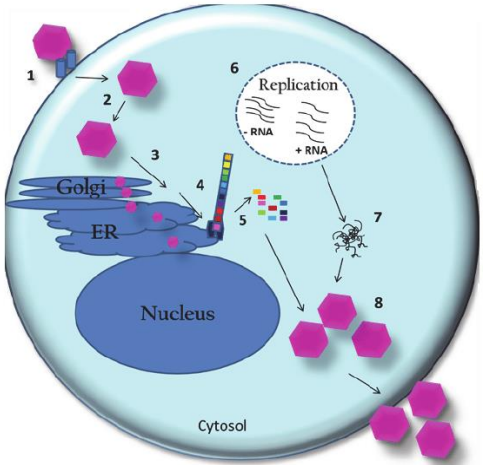

Fig. 3: Viral life cycle of Coxsackievirus A16 (Pamela *et al*., 2011).

bll2-cII loop's two "switcher" residues, Tyr89 and Glu88, cause a conformational shift. The conformational change and substrate selectivity of the coxsackievirus A16 2A protease were brought about by this switch (Wald, 2009).

Life cycle of Coxsackievirus A16

The general host and virus components suggested to contribute to production of new coxksackie-virus (Fig. 3) are as follows (Baggen *et al*., 2018):

- Viral entry through binding coxsackievirus and adenovirus receptor (CAR) and decay accelerating factor (DAF).

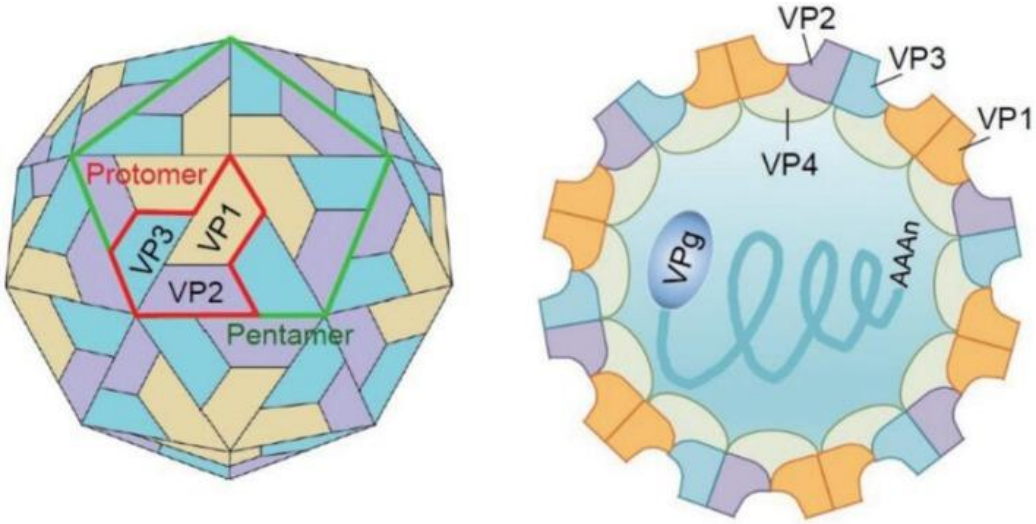

Fig. 4: Anatomical structures of the Enterovirus A71 (EV-A71) (Yuan *et al*., 2018).

- Internalization and transport of viral particles to the Golgi and endoplasmic reticulum (ER).
- viral uncoating,
- release of viral RNA, translation of RNA by ribosomes on the rough endoplasmic reticulum (ER) into viral polyprotein,
- autocleavage of polyprotein into viral structural and functions proteins.
- positive and negative strand RNA transcription to replicate viral genome.
- release of viral genome into the cytosol to encapsidate with structural proteins.
- Formation and release of viral progeny- The virus releases its positive-sense genome into the cytosol for transcription and translation as soon as it uncoils and enters the cytosol. Following translation at the rough endoplasmic reticulum (ER), a polyprotein consisting of the viral proteins VP4, VP3, VP2, VP, 2A, 2B, 2C, 3A, 3B, 3C, and 3D is broken down into its constituent structural and functional proteins. An RNA-dependent RNA polymerase called 3D pol is virally encoded and transcribes (Cihakova, 2011).

Anatomy of Enterovirus A71 (EV-A71)

EV-A71 belongs to the Picornaviridae family's Enterovirus genus, species A. The icosahedral, non-enveloped capsid of the EV-A71 (Fig. 4) particle is symmetrical and measures 20–30 nm. The viral genome is made up of a single-stranded positive-sense RNA with one open reading frame (ORF) and is roughly 7,500 nucleotides long. It is encircled by a highly organised 5′-untranslated region (5′UTR) and a 3′UTR with a poly(A) tail. After the polyprotein is further broken down, three precursor proteinsP1, P2, and P3 are created (Xu *et al*., 2014).

VP1, VP2, VP3, and VP4 are the four structural viral proteins that emerge from the breakdown of P1 precursor protein. These four proteins combine to form a protomer. Five of these protomers make up a pentamer, and when 12 pentamers come together, a virion with the viral DNA is created. Although VP4 is contained inside the capsid, VP1, VP2, and VP3 are visible on its exterior (Hu *et al*., 2023).

Life cycle of Enterovirus A71 (EV-A71)

Steps involved in the Life cycle of Enterovirus A71 (EV-A71) (Fig. 5):

- It first attaches to the host cell surface by binding of the viral capsid proteins to the cell surface receptors and entering the host cell through endocytosis.

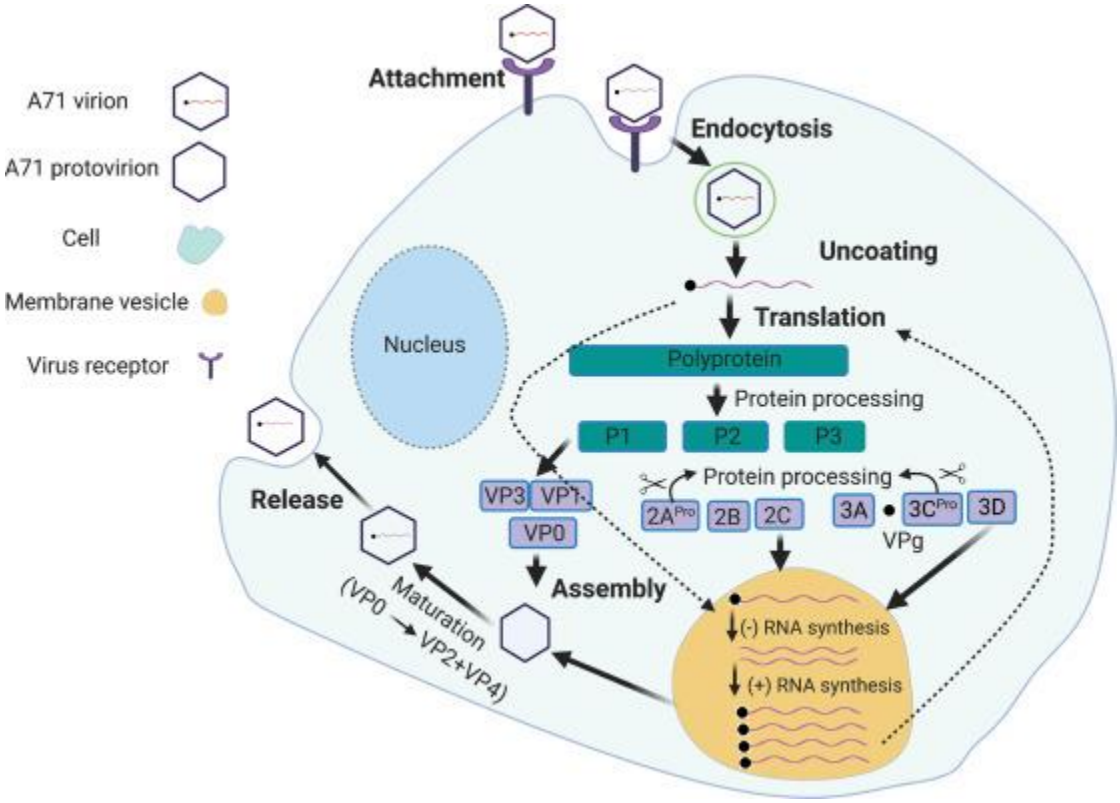

Fig. 5: Life Cycle of Enterovirus A71 (EV-A71) (Wang *et al*., 2022).

- The uncoating of EV-A71 is triggered upon its binding to the host cell receptor through a distinctive hydrophobic pocket in the capsid.
- Next, the viruses undergo uncoating and release of the viral genome RNA in the cytoplasm. The released positive viral genome RNA is used as a template for the replication of viral genome RNA and translation of the viral polyprotein. The polyprotein is then proteolytically cleaved into structural proteins (VP0, VP1 and VP3) and nonstructural proteins (2A, 2B, 2C, 3A, 3AB, 3C, 3CD) by viral proteases 2A and 3C (Shingler *et al*., 2013).
- Genome replication is catalyzed by the viral RNA-dependent RNA polymerase ($3D^{pol}$), and a negative-strand RNA is first synthesized, which serves as a template for synthesis of positive-sense viral genome RNA (Yuan *et al*., 2018; Melia *et al*., 2019).
- Nascent positive RNA molecules either serve as templates for viral polyprotein translation or negative-strand RNA synthesis, or are encapsidated into progeny virions
- Virion assembly starts with one copy of each VP0, VP1 and VP3 self-organizing into protomers, with five copies of protomers forming a pentamer (Jiang *et al*., 2014). Together with nascent viral RNA, twelve copies of pentamer form the provirion, which are converted into mature virion upon the cleavage of VP0 into VP4 and VP2.

Other Diseases caused by the causative virus

- Acute haemorrhagic conjunctivitis (A24 specifically),
- Herpangina,
- Meningitis (both Coxsackie A and B viruses).
- Paralytic poliomyelitis.

Prevention of tomato flu

- Avoid making direct touch with the diseased

individual.

- Do not shake hand, play, or hug any youngster who exhibits tomato fever symptoms.
- Keep them hydrated by drinking plenty of water, milk, juice and soup.
- Clean and sanitized your children's utensils, clothes, toys, and other belonging regularly.
- Bathe or clean with warm water.
- Include immunity boosting and nutrient dense items in your child diet.
- Instruct kids to use a handkerchief when sneezing or coughing if they have a runny nose or cough.
- Refrain from rubbing or scratching the blister, and wash your hands thoroughly after handling it. You should see a doctor if your child is fewer than six months old and has a weakened immune system.

Strategies for alleviate the tomato flu outbreak in India

Several crucial tactics can be used to successfully contain the tomato flu outbreak in India. To identify and isolate affected persons, it is first necessary to create strong surveillance and contact tracing protocols. This entails keeping a tight eye on patients, tracking down close contacts, and testing as soon as possible to stop the spread of the infection. Second, programmes for public health education should be started to spread knowledge about the tomato flu and encourage the use of preventative measures such as frequent hand washing, avoiding close contact with sick people, and maintaining respiratory hygiene. To manage the strain on healthcare institutions, strengthening the infrastructure is essential (Ahmed *et al*., 2023).

For tomato flu cases to be managed effectively, there must be a sufficient allocation of resources, including medical supplies and PPE. The goal of research should be to gain a deeper comprehension of the virus, its dynamics of transmission, and possible therapeutic approaches. Furthermore, in order to shield vulnerable populations and stop future epidemics, vaccine development needs to be given top priority. For a coordinated and successful containment strategy, international cooperation with health organisations as well as ongoing monitoring and assessment of the outbreak response are essential. These steps can be taken to stop the tomato flu from spreading and protect India's public health (Sun *et al*., 2022).

Conclusion

The news of yet another new virus making the rounds may seem a bit overwhelming, but it's crucial to keep in mind that this one is not deadly and is not spreading widely. It is extremely possible to keep it under control if you exercise appropriate caution and vigilance. It was eventually determined that a variation of CV-A16 was the origin of the recent "tomato flu" pandemic in India, which was characterised by huge red blisters in the hand, foot, and buttocks. As a result, the phrase "tomato flu" has been abandoned and is now recognised as another HFMD outbreak. In summary, prompt preventive actions are critical to managing the disease and preventing new outbreaks (Ismail *et al*., 2023). These include upholding appropriate hygiene and sanitation standards and instituting a five-to seven-day period of isolation after the disease has been contracted. Despite the lack of proven antivirals for HFMD, acyclovir and oseltamivir have demonstrated efficacious outcomes by mitigating the intensity of symptoms. Immunoglobulin therapy has also been demonstrated to lengthen the clinical cure period and reduce mortality in HFMD patients. Only EV-A71 is protected against by the three HFMD vaccines that are currently licenced. Therefore, the most effective preventive measure may involve developing a multivalent vaccine against many HFMD aetiologies, including CV-A16.

Author Contributions

All authors contributed to the conceptualization, literature review, analysis, drafting, and critical revision of the manuscript ensuring its accuracy and completeness. All authors have read and

agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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