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A PITHY MEMORANDUM ON TOMATO FLU

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Abstract: The emergence of Tomato Flu, initially in Kerala, India, presents a rare viral infection primarily affecting children under five. Though non-life-threatening, its symptoms mirror those of COVID-19, complicating diagnosis. The disease, erroneously named for its tomato-like blisters, is linked to Chikungunya-carrying mosquitoes. Coxsackievirus A16, a major cause of Hand, Foot, and Mouth Disease, plays a pivotal role. The virus's genome, comprising non-coding, structural, and non-structural regions, orchestrates replication through intricate processes. Human scavenger receptor class B, membrane 2, acts as a cellular receptor. The replication cycle involves translation, proteolytic processing, and replication of viral RNA, ultimately leading to infectious particles. Epidemiologically, Tomato Flu's transmission, prevalent in Asian Pacific countries, is facilitated by faecal-oral route, direct contact, and respiratory droplets. In 2022, it surfaced in Kerala, spreading across India's northeast. Clinical features include fever, rashes, joint pain, and distinctive tomato-like blisters. Diagnosis relies on clinical observations, viral isolation, serology or molecular studies. While treatment is symptomatic, no specific anti-viral exist. Prevention emphasizes hygiene, vaccination, and hospital infection control. A growing understanding of Tomato Flu requires ongoing monitoring and research for effective management and prevention.

Keywords: Coxsackievirus A16, Covid 19, Chikungunya, Hand Foot Mouth Disease [HFMD], Tomato flu, Tomato fever, Misonomer, Picornaviridae, Viral infection.

I. INTRODUCTION

Hand, Foot, and Mouth Disease (HFMD) caused by Coxsackievirus A16 (Cv-A16) stands as a recurrent public health concern, particularly in Asian Pacific countries. This viral infection, a member of the Human enterovirus (HEv-A) species within the Picornaviridae family, exhibits a unique genomic structure characterized by non-coding, structural, and non-structural regions. The transmission dynamics involve faecal-oral route, direct contact, and respiratory droplets, contributing to periodic outbreaks.

Cv-A16's genome, a single-stranded, positive-sense RNA, undergoes a complex replication process upon entering permissive host cells. The virus utilizes human scavenger receptor class B, membrane 2 (hSCARB2) as a candidate cellular receptor. Replication entails translation, polyprotein processing, and RNA replication mediated by viral proteins, with specific emphasis on the 5'UTR and internal ribosome entry sites (IRESs). The virus primarily affects humans, showcasing a predilection for skeletal muscles and, intriguingly, demonstrating tropism to lung and brain tissues in animal models.

In the epidemiological landscape, periodic outbreaks have been observed in various Asian Pacific countries, highlighting the contagious nature of HFMD. Recent reports from India have identified a distinct manifestation termed "Tomato Flu," caused by Cv-A16, emphasizing the need for ongoing research and surveillance. The transmission modes, including close contact and the survival of the virus on environmental surfaces, necessitate a comprehensive approach to public health, emphasizing handwashing, hygiene, and environmental cleanliness.

Clinical features of Cv-A16 infection encompass fever, rashes, body aches, and characteristic fluid-filled blisters, notably resembling tomatoes. The recent emergence of Tomato Flu in India, reported in 2022, has raised concerns due to its spread across different states and its impact on children under five. Laboratory diagnosis involves clinical examination, viral isolation, serology, and molecular studies, enabling a thorough understanding of the disease.

Management of Cv-A16 infections currently revolves around symptomatic relief and hygiene measures, as no specific antiviral treatment exists. Prevention strategies include general precautions, vaccination, and stringent hospital infection control. As the global community grapples with the challenges posed by emerging infectious diseases, understanding the etiology, replication mechanisms, and epidemiology of Cv-A16 becomes crucial for effective public health responses.[4]

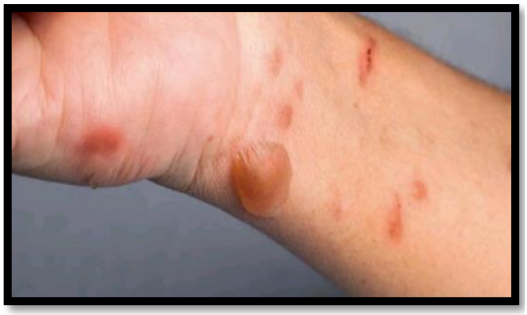

Fig:1. Vesiculobullous blister in a patient with 'tomato flu'.[4]

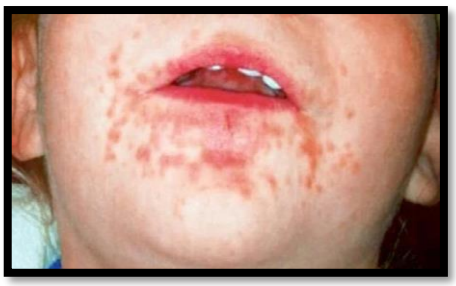

Fig: 2 Macules, Papules and Vesicles around the mouth of a child due to HFMD.[22]

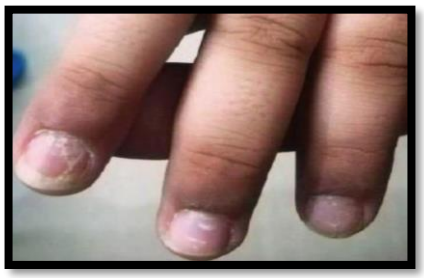

Fig:3 Nail Changes of Onychomadesis of index finger nail, leukonychia and mild dystrophy of other nails in a 5 years old child seen 2 months after Tomato Flu.[39]

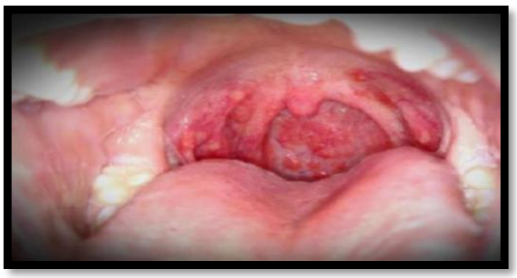

Fig:4 Oral ulceration in a patient with tomato flu [37]

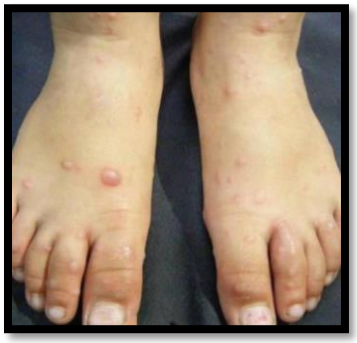

Fig:5 Small multiple/round/oval macules and pearly white vesicles with a red areola dorsum of feet in a 5 years old child.[39]

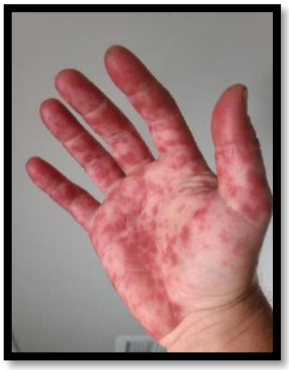

Fig:6 Maculopapular rash on the palm of Tomato Flu patient.[22]

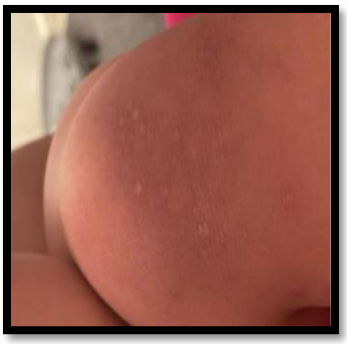

Fig:7 Healing lesions after 16 days of rash, with little or no scarring.[43]

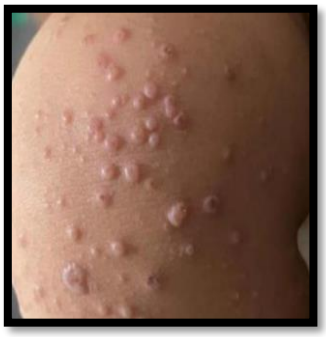

Fig:8 Fleshy vesicular lesions on leg of the 13-month-old girl after 4 days of infection.[43]

II. ETIOLOGY

Coxsackievirus A-16 (Cv-A16) is a member of the enterovirus genus, part of the Picornaviridae family. This virus is recognized as a primary causative agent of Hand, Foot, and Mouth Disease (HFMD), a common viral illness affecting predominantly infants and young children.[9]

The etiology of Cv-A16 involves several key aspects, including its genetic makeup, cellular receptors, and the viral replication process. The virus is characterized by a single-stranded, positive-sense RNA genome, which serves as a template for both translation and replication upon entering a host cell.

One critical cellular receptor for Cv-A16 is the human scavenger receptor class B, membrane 2 (hSCARB2). This receptor plays a pivotal role in initiating the virus's replication cycle, binding to a specific downturn in the viral capsid known as the gulch. The canyon surrounding the five-fold axis of symmetry facilitates the entry of the virus into the host cell.

Once internalized, the viral RNA is released into the host cell's cytoplasm, where it serves as a template for translation. This process results in the production of a viral polyprotein, a precursor to both structural

and non-structural viral proteins. The polyprotein is further processed by viral proteases (2Apro and 3Cpro), releasing stable precursors and individual proteins crucial for the virus's replication.

The replication of Cv-A16's RNA genome is orchestrated by non-structural proteins, P2 and P3, and involves a complex series of steps. The RNA-dependent RNA polymerase 3Dpol plays a key role in initiating and mediating the elongation of the viral genome. The replication process includes uridylation of the protein primer VPg, utilizing a secondary RNA structure known as cis-acting replication element (cre) as a template.[10] Negative-strand RNA intermediates are produced during replication, serving as templates for the synthesis of positive-stranded RNA molecules. These positive-stranded RNAs can either undergo another round of translation and replication or be packaged into capsids to form infectious virus particles. The release of these new virus particles occurs through cell lysis and various nonlytic mechanisms.

In terms of epidemiology, Cv-A16 has been associated with outbreaks of HFMD, with periodic occurrences in Asian Pacific countries such as China, Japan, Singapore, Malaysia, and others. Transmission primarily occurs through the faecal-oral route, direct contact, and respiratory droplets. Maintaining hygiene, including handwashing, has been shown to decrease the incidence of HFMD.

Understanding the etiology of Cv-A16 is crucial for developing preventive measures, such as vaccines. While no specific antiviral treatment is available for Cv-A16, preventive strategies include maintaining good personal hygiene, vaccination, and hospital infection control. Vaccination, particularly with an inactivated vaccine, has been recommended for children to enhance immunization and reduce the impact of outbreaks.

In conclusion, Coxsackievirus A-16, as the causative agent of HFMD, exhibits a well-defined etiology involving genomic characteristics, cellular receptors, and a complex replication process. Studying these aspects is vital for comprehending the virus's behavior and developing effective preventive and therapeutic strategies.[10]

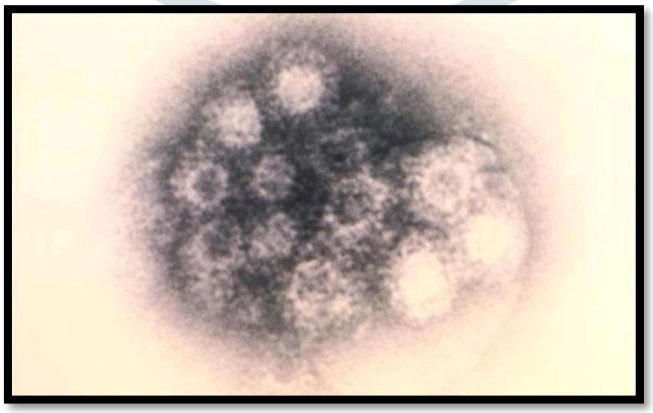

Fig:9 Electronic micrograph of 'tomato flu' causing agent, Coxsackievirus.[10]

THE REPLICATION OF COXSACKIEVIRUS A16 (CV-A16) INVOLVES FOLLOWING KEY STEPS:

1. **Receptor Binding and Entry**
   - The virus binds to a specific cellular receptor, such as human scavenger receptor class B, membrane 2 (hSCARB2).
   - The receptor interaction initiates the viral replication cycle by binding at a downturn in the capsid known as the gulch.[11]
2. **Release of Viral RNA into Cytoplasm**
   - Upon entry into the host cell, the viral RNA is released into the cytoplasm.
3. **Translation and Polyprotein Production**
   - The viral RNA serves as a template for translation, producing a polyprotein.
   - This polyprotein is then proteolytically processed by viral proteases 2Apro and 3Cpro.
4. **Structural and Non-structural Protein Release**
   - The processed polyprotein releases structural and non-structural viral proteins.
   - Non-structural proteins, P2 and P3, play a role in viral genome replication.
5. **RNA Genome Replication**
   - Replication of the RNA genome is initiated by uridylation of the protein primer VPg.
   - Viral RNA-dependent RNA polymerase 3Dpol, using a secondary RNA structure called cis-acting replication element (cre) as a template, synthesizes negative-stranded intermediates.[42]
6. **Positive-stranded RNA Synthesis**
   - 3Dpol mediates the elongation of VPg to produce positive-stranded RNA molecules.
7. **Capsid Formation**
   - Capsid proteins are formed, contributing to the assembly of the viral capsid.[16]
8. **Packaging of RNA**
   - Positive-stranded RNA molecules are packaged under the capsid.
9. **Formation of Infectious Viral Particles**
   - Capsid proteins and RNA together form infectious viral particles.
10. **Release of New Viral Particles**
    - New viral particles are released through cell lysis and various nonlytic mechanisms.

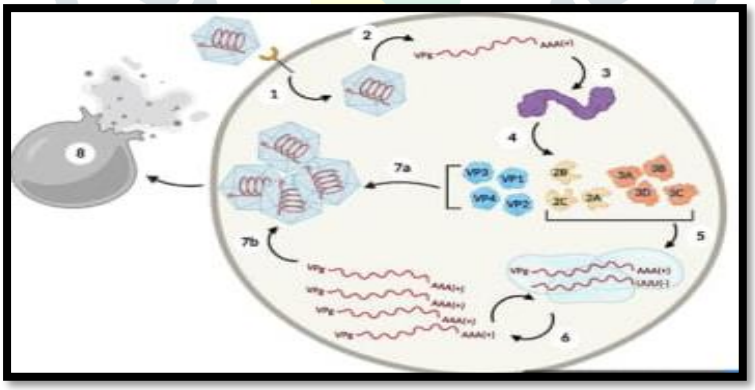

Fig: 10 Schematic diagram of the viral replication process.[42]

III. EPIDEMIOLOGY

The epidemiology of Tomato Flu, caused by Coxsackievirus A-6 and A-16 (Enterovirus), spans several decades and countries, showcasing its global impact. In 1959, the first case of Hand, Foot, and Mouth Disease (HFMD), associated with EV-71, was described in Birmingham. Subsequently, Asian Pacific countries, including China, Japan, Singapore, Malaysia, Australia, Cambodia, Taiwan, Thailand, South Korea, and Vietnam, witnessed periodic outbreaks, typically every two to three years.

Transmission occurs through the faecal-oral route, direct contact, and respiratory droplets, with a Guangdong study suggesting a predominant faecal-oral route in China. The virus's survivability on surfaces contributes to its contagious nature. 'Tomato flu' gained attention for its contagiousness, and maintaining hygiene, handwashing, and cleanliness have been proven to reduce HFMD incidence.

Globally, in 1957, Toronto identified Cv-A16, linked to Tomato Flu, characterized by epidemic and erratic patterns. Neurological disorders and mortalities resulted from this infection [17].EV-71 emerged in the Netherlands in 1963 and was first isolated in California, USA, in 1969. China faces a substantial health burden due to HFMD, leading to the classification of EV-71 as a notifiable disease.[20]

Cv-A16 exhibits three genotypes: A, B, and C. Predominant circulating sub-genotypes include B1a and B2b in Australia, Malaysia, and mainland China. Unique sub-genotypes like B1c and B2c surfaced in France (2005-2010) and Malaysia (2003-2007). Outbursts in Vietnam, Thailand, Malaysia, and India highlighted the virus's geographical spread [17]

In May 2022, a Tomato Flu epidemic emerged in India, starting in Kerala and later spreading to other states. The Lancet Respiratory Medicine reported 82 cases in Kerala, primarily affecting children under five. Symptoms include fever, rashes, body pain, and gastrointestinal issues, with distinctive tomato-like blisters.[16]

Laboratory diagnosis involves clinical evaluation, viral isolation, and molecular studies. The absence of specific treatment makes symptom management crucial, focusing on hydration, fever control, and isolation. Recent research explores potential antivirals and vaccines.[24]

Preventive measures encompass general hygiene, vaccination (inactivated EV A71 vaccine), hospital infection control, and public awareness. Timely isolation, sanitation, and educating children on hygiene are critical preventive strategies.[22]

Understanding Tomato Flu's epidemiology aids in developing targeted interventions and global collaboration to mitigate its impact on public health. Ongoing research aims to enhance diagnostic methods, treatment options, and preventive measures against this contagious viral infection.

Fig: 11 A map showing the Indian States where most cases of Tomato Flu were identified.[31]

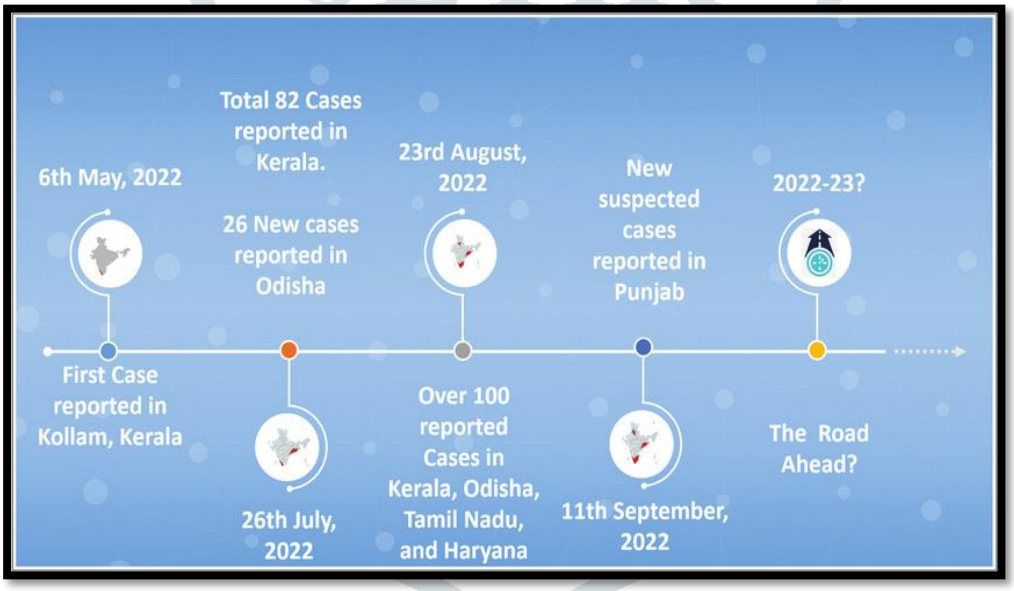

Fig:12 A Timeline of Tomato Flu outbreak across India.

IV. DIAGNOSIS

1. **Clinical Diagnosis**
   - Tomato Flu is largely diagnosed based on clinical features, especially the presence of high fever, joint pain, and rash.
2. **Laboratory Tests**
   - Viral Transport Medium is used for collecting samples within 48 hours of illness.
   - Throat, stool, and skin scrapings are collected as part of an outbreak investigation.
   - For patients with encephalitis, cerebrospinal fluid (CSF) samples are collected within 48 hours.[30]
3. **Viral Isolation**
   - Viral isolation is considered a gold standard in the diagnosis of Hand, Foot, and Mouth Disease (HFMD), to which Tomato Flu is related.

- Isolation is performed on Vero Rhabdomyosarcoma and MRC 5 monolayers.
- Presence of cytopathic effect increases suspicion of enterovirus, confirmed by immunofluorescence assay. [21]

4. Serological Studies

- Serological studies may be performed to measure neutralizing antibody titres specific to the serotype.
- A four-fold increase in titres is considered significant.
- Serology is not as sensitive but may be used to monitor recovery.[30]

5. Molecular Diagnosis - RT-PCR

- With the advent of molecular diagnosis, Reverse Transcription Polymerase Chain Reaction (RT-PCR) is increasingly preferred.
- RT-PCR is used for laboratory confirmation and is performed using 5' - UTR for characterization and VPI region for genotyping.[30]

6. Other Molecular Studies

- Molecular studies may include genotyping using viral capsid subunit proteins (VCSP) of Vp4 and Vp1 genes. Genotyping aids in understanding the specific strain and its characteristics.

V. TREATMENT

Recent research indicates that Acyclovir has been under clinical trials and has shown effectiveness in lowering fever and improving skin condition within 24 hours. No licensed antivirals are available for Tomato Flu treatment.[37]. Constant monitoring is required to understand the evolution of the disease and the need for healthcare intervention. Complications or mortalities related to Tomato Flu are not reported, but vigilance is essential. Mention of a strain-specific inactivated virus aluminium adjuvant vaccine developed to reduce the severity of Tomato Flu in affected individuals.

1. General Management

-Tomato Flu is considered a rare infectious disease, and as of now, no specific drugs are available for its treatment.

- Symptomatic management is primarily focused on relieving symptoms and supporting the patient through the illness.[1]

2. Fever and Pain Management

- Antipyretics and analgesics are used for managing fever and pain.
- Commonly used medications include Ibuprofen or Acetaminophen.[1]

3. Fluid Intake

- Due to the significant risk of dehydration, maintaining adequate fluid intake is crucial.
- Recommendations include water, juice, or milk to prevent dehydration.[1]

4. Hygiene and Isolation

- Infected children are isolated or quarantined for 5 - 7 days to prevent transmission to others.
- Emphasis on proper hygiene practices to control contamination and spread. [1]

5. Specific Measures

- No specific antiviral treatment is available for Tomato Flu.
- Antimicrobials are considered useless unless blisters become infected.[19]

6. Hospitalization

- Hospitalization may be required in cases of excessive dehydration or the development of neurologic or cardiopulmonary problems.[37]

7. IV Immunoglobulin

- IV immunoglobulin is not suggested for Tomato Flu treatment.[37]

8. Topical Agents

- Lidocaine topically applied orally is mentioned but not recommended for children due to potential harm.[37]

9. Gargle Agent

- A gargle agent is formed by combining liquid Ibuprofen and liquid Diphenhydramine, which helps coat ulcerations and relieve pain.[19]

VI. PREVENTION

1. Health Department Measures

- The Health Department enforces preventive steps to control the contamination and spreading of Tomato Flu in the public.

2. Isolation

- Infected individuals are isolated for 5 - 7 days to prevent the transmission of the virus to others.

3. Public Awareness

- Public awareness campaigns are conducted to educate the community about Tomato Flu.
- Advice is given to maintain proper hygiene practices, sanitize, and quarantine affected individuals and their belongings.

4. Hygiene Practices

- Emphasis on maintaining proper hygiene to reduce the risk of transmission.
- Handwashing and cleaning are shown to decrease the incidence of Hand, Foot, and Mouth Disease (HFMD), which Tomato Flu is related to.

5. Geographic Spread Monitoring

- Constant monitoring of the geographic spread of Tomato Flu is essential.
- Awareness campaigns and preventive measures are extended to areas where outbreaks occur.

6. Fluid Transmission Routes

- Given that Tomato Flu is reported as contagious, measures are likely taken to minimize transmission routes, including direct contact and respiratory droplets.

7. Vaccine Development

- Mention of a strain-specific inactivated virus aluminum adjuvant vaccine developed to reduce the severity of Tomato Flu.
- Vaccination efforts may be a key preventive strategy, although details about the vaccine's availability and distribution are not provided in the abstract.[27]

8. Government Action

- The government enforces actions on infected people to ensure proper isolation for a specified period, guiding symptoms.

9. Awareness of Transmission Routes

- Public awareness efforts include informing individuals about the modes of transmission, such as direct contact and lack of hygiene.

10. Monitoring and Reporting

- Regular monitoring and reporting of Tomato Flu cases to track the spread and take timely preventive actions.

CONCLUSION

These details highlight various preventive measures, including public awareness, hygiene practices, isolation, vaccination efforts, and government actions to control the spread of Tomato Flu. The emphasis on both individual and community-level preventive strategies is evident.

In conclusion, the emergence of "Tomato Flu" in India, caused by Coxsackievirus A16, has presented significant public health challenges, particularly among children under five to nine years old. The disease, characterized by painful blisters resembling small tomatoes, has spread rapidly, prompting extensive research into its virology, transmission, clinical manifestations, and management. While no specific treatment or vaccine is currently available, supportive care and hygiene practices remain essential in controlling the spread of the disease.

Furthermore, ongoing surveillance and research efforts are crucial for better understanding and effectively managing this viral outbreak. Implementing preventive measures such as vaccination, maintaining good personal hygiene, and proper sanitation are vital steps in mitigating the impact of Tomato Flu and preventing future outbreaks.

Collaborative efforts between healthcare authorities, researchers, and the community are imperative in tackling this public health issue and safeguarding the well-being of the population.

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