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"UNDERSTANDING TOMATO FLU": A NEW VIRAL INFECTION LINKED TO COXSACKIEVIRUS A16 - CURRENT INSIGHTS AND FUTURE PROSPECTS

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1. INTRODUCTION

Tomato flu is an infectious disease that is caused by an unexplained viral organism detected first in Kerala, India in May 2022. The infection was named 'Tomato flu' due to its main symptom, the tomato-shaped blisters all over the body.[1] The presentation initially starts as a red-coloured small blister which then enlarge to resemble the shape of a tomato, hence the name 'Tomato flu', also synonymously known as 'Tomato fever.[2] It predominantly affects children below the age of 5 years. Strong immunity against the tomato flu virus might be the reason for its low incidence in adults.[3] However, adults might act as carriers transmitting the virus while handling the children. Tomato flu is considered to be a **"Hand, Foot, and Mouth disease"(HFMD),** the common viral infection according to Dr. Amar S Fettle, Epidemiologist and State Nodal Officer of Kerala.[4] HFMD is caused by viruses that belong to the enterovirus genus such as polioviruses, coxsackie viruses, echo viruses, and other enteroviruses. Coxsackie virus A16 is the most frequent cause of HFMD. Coxsackie virus A16 infection produces only a mild form of the disease in HFMD Without medical care, almost all patients recover in about 7 to 10 days.[5] It is frequently confused with foot-and-mouth disease, also known as hoof-and-mouth disease, which affects cattle, sheep, and swine. The two illnesses, however, are unrelated as they are brought on by different viruses. Infection is transmitted from one person to another by direct contact with the infectious virus, which is present in the saliva, blister

fluid, nose and throat secretions, and stool of those who are infected. The virus is most frequently transferred by people's hands, fomites, and by contact with surfaces that have been exposed to the virus. Even though infected people typically show no symptoms in the first week of the sickness, they are most contagious during that time. HFMD is n 32Most patients have only minimal clinical characteristics. Since enteroviruses are widespread, adults and older children are likely to be immune. Respiratory droplets, contact with blister fluids, and contact with contaminated faeces are the three main routes that enterovirus is spread.[6]

By avoiding contact with sick individuals and maintaining personal hygiene, the possibility of transmission can be reduced. Adults, including pregnant women, are more susceptible to infection if they have never been exposed to these viruses' protective antibodies. Most enterovirus infections during pregnancy result in mothers having a minor or no illness. There is currently no definite evidence that maternal enterovirus infection can cause untoward pregnancy outcomes such as abortion, stillbirth, or congenital abnormalities. However, mothers who contract the virus just before giving birth may pass it to the newborn.[7]

The likelihood of infection is higher in a new-born whose mother is experiencing enterovirus disease symptoms at the time of birth. The majority of new-borns who contract an enterovirus have a minor illness, but in rare circumstances, they may develop a serious infection in several vital organs, including the liver and heart, and could die as a result of the infection.[8]

However, researchers are still looking into the precise etiological factor that is causing this infection.

Tomato flu is naturally benign viral infection for the children and was firstly developed in 1948. The two major disease-causing pathogens responsible for tomato flu are coxsackievirus A16 (CV-A16) and huma enterovirus 71(EV-71). It is a slight viral infection linked with self-restraining clinical features recovered within 5 to 7 days. Tomato flu as HFMD (Hand, Foot and Mouth Disease) didn’t get much severity for a long duration. Though, Tomato flu attracted much more consideration due to its ascending number of cases throughout the past years that HFMD shows the unusual different symptoms. (Ismail A., 2022) On global level tomato flu is named as HFMD (Hand, Foot and Mouth Disease), was rapidly spreading amid young adolescents. CV-A16 is the main pathogen causing ‘Tomato Flu’. Since, it is thought to be contraindicated and the medical features of disease is considered to be unusual demonstration of HFMD. (Carmona RCC., 2022)

Fig. 1: Vesiculobullous blister in a patient with 'tomato flu.'[9]

Historically, Tomato flu is regarded as a benign viral infection in children and was first reported as early as 1948. The two major disease-causing pathogens identified are Coxsackievirus A16 (CV-A16) and Human Enterovirus 71 (EV-71). The infection is self-limiting and usually resolves within 5 to 7 days. Though Tomato flu or HFMD had not shown severe outcomes for a long time, it has recently gained global attention due to an increasing number of cases and unusual clinical symptoms compared to classical HFMD.[10]

On a global level, Tomato flu is recognized as a variant of HFMD (Hand, Foot, and Mouth Disease), spreading rapidly among young children and adolescents. Coxsackievirus A16 remains the primary pathogen responsible for Tomato flu. Since the medical and clinical characteristics differ slightly from typical HFMD, this infection is now being viewed as an unusual and emerging variant, attracting more scientific investigation and public health concern.[11]

2. ETIOLOGY

- Some reports say that the cause of tomato flu or fever might be HFMD, caused by the family of enteroviruses that are known to commonly affect children and adults with weaker immunity.[12] An RNA virus from the Picornaviridae family known as Coxsackie virus A16 was shown to be the cause of tomato flu.[13]
- According to British Medical Journal report it was found that it is not a distinct virus but coxsackie virus A16. Samples of two children were collected by swabs who returned from India with tomato flu were found positive of coxsackie virus A16.[14]
- To try to determine the source of the illness, scientists have been investigating swabs from children suffering from tomato flu. The findings of the lab tests showed that the children had the enterovirus coxsackie A16.[15]

- Therefore, it appears that Disease has been indeed tomato flu. It is not a sort of influenza, has nothing to do with tomatoes, and is not even remotely a novel illness.[16]

3. EPIDEMIOLOGY

Tomato flu as HFMD (Hand, Foot and Mouth Disease) causing virus CVA16 was identified for the first time in Toronto in 1957 globally; it was described to be epidemic and erratic cases. While, CVA16 spread mostly in nature. By the time this infection resulted in severe neurological disorders leading to mortalities.

During 1963, in Netherlands EV71 began socializing and in 1969, in California, USA it was isolated for the first time. Meanwhile during recent years of spreading worldwide EV71 has started its circulation by epidemics mainly occurred in Asia-Pacific regions, counting China, Malaysia and Japan. In China it caused as HFMD (Hand, Foot and Mouth Disease) forming sickness burden over the health sector.

Hence the eruption of EV71 in Anhui, on May 2008, included in the class C notifiable disease, as its morbidity and fatality rate were severe to be at forefront in notifiable infectious disease. Among Southeast China, Beside Yangtze River Delta region, Zhejiang ranked in top three places of HFMD outbreak.

Fig. 2: Epidemiological manifestation of Tomato Flu showing erythematous rashes on the palm.[17]

The remarkable thing about this disease is that in spite of any major hitches or any mortality rate this disease can be very painful with new variant. Though the disease is of contagious nature, the Health Department of Kerala Government enforced adequate preventive steps to control the contamination and spreading of disease in public. Awareness among society has been advised to maintain proper hygiene and sanitization as well as quarantine the infected person and belongings, although, government enforced action on infected for isolation for 5-7 days with proper guidance on symptoms.

Tomato Flu was first detected in India on May 2022 in Kerala state and was identified as a viral organism. It derived its name 'Tomato Flu' from the major symptom of blisters in tomato shape appearing over every part of body. It is also called 'tomato fever' and 'tomato influenza' resembling to the oval shape like tomato. In Kollam district of Kerala state almost eighty-two patients were affected in July, 2022 due to disease outspread. The number of cases might be increased with the time.

4. SIGN AND SYMPTOMS

1. Fever: The illness often begins with a high-grade fever, which is usually the first symptom noticed in infected children.[18]

2. Painful red blisters or rashes: After fever onset, red, fluid-filled blisters appear on various parts of the body — including hands, feet, mouth, buttocks, and sometimes the legs or arms. These resemble the blisters seen in HFMD and are often painful or itchy.[19]

3. Body pain and joint swelling: Children may experience muscle pain, joint swelling, and general body aches. This causes irritability and difficulty in walking or playing.[20]

4. Fatigue and weakness: Infected children frequently show lethargy, tiredness, and reduced appetite.[21]

5. Nausea, vomiting, and diarrhea: Some cases include mild gastrointestinal symptoms like nausea, stomach pain, and diarrhea.

6. Cold-like symptoms: A few patients develop runny nose, sneezing, or cough, similar to common cold symptoms.

7. Dehydration: Due to fever, vomiting, and mouth blisters (which make eating or drinking painful), children may suffer from dehydration.

8. Skin discoloration: In some cases, dark patches or discolored skin are seen on the hands, knees, or buttocks after the blisters heal.[22]

Fig. 3: Skin rashes and blisters on legs – a symptom of Tomato Flu.[23]

5. DIAGNOSIS

Tomato flu, also known as Tomato Fever, is a self-limiting viral illness that primarily affects young children below the age of 10 years. It was first reported in Kerala, India, in May 2022, and later cases were identified in Tamil Nadu, Odisha, and other Indian states. The disease derives its name from the characteristic red, tomato-shaped blisters that appear on the body during infection. Although initially confused with dengue or chikungunya, the diagnosis of tomato flu relies on a combination of clinical examination, symptom assessment, and laboratory testing to rule out other similar viral infections.[24]

1. Clinical Diagnosis

The first step in diagnosing tomato flu is a detailed clinical evaluation based on symptoms and physical signs.

- ✓ Common clinical features include:
- ✓ Fever (moderate to high)
- ✓ Painful, red blisters resembling small tomatoes
- ✓ Skin rashes and irritation
- ✓ Fatigue and body pain
- ✓ Dehydration
- ✓ Cough, cold, and nausea in some patients

Physicians generally make a provisional diagnosis when these symptoms appear in young children during local outbreaks and after eliminating other common viral diseases.

The presence of round, red blisters (2–4 cm in size) and skin irritation on the hands, feet, and mouth are hallmark features.[25]

2. Differential Diagnosis

Diseases that must be ruled out include:

- ✓ Hand, Foot, and Mouth Disease (HFMD) caused by Coxsackie virus
- ✓ Since tomato flu shows symptoms similar to other viral infections, Dengue fever
- ✓ Chikungunya
- ✓ Zika virus infection
- ✓ Chickenpox

The similarity in rashes and fever pattern often causes confusion, so laboratory testing plays an important confirmatory role.[26]

3. Laboratory Diagnosis

Although tomato flu is mainly diagnosed clinically, laboratory tests are used to exclude other infections rather than confirm tomato flu specifically, since no single diagnostic test exists for the condition yet.

a. Blood Tests

- ✓ Complete Blood Count (CBC): To check for leukopenia or thrombocytopenia (common in dengue but not in tomato flu).
- ✓ Liver Function Tests (LFTs): To assess liver enzyme changes.
- ✓ Serological tests for dengue (NS1 antigen, IgM/IgG) and chikungunya help in differentiation.

b. Viral Detection Tests

- ✓ RT-PCR (Reverse Transcriptase Polymerase Chain Reaction):
- ✓ Used to test samples for dengue, chikungunya, zika, or enterovirus.
- ✓ If all results are negative but clinical symptoms persist, tomato flu is considered probable.

c. Swab and Stool Samples

In children, stool or throat swabs can be taken to detect enteroviruses that may be linked to the disease.

4. Imaging and Other Tests

Generally, no imaging studies are required. However, in severe cases with dehydration or secondary infection, basic imaging (chest X-ray or ultrasound) may be done to rule out complications.

5. Confirmatory Diagnosis

There is currently no specific confirmatory test for tomato flu.

Diagnosis is mainly based on:

- ✓ Clinical presentation
- ✓ Exclusion of other viral infections
- ✓ Epidemiological link (recent exposure or outbreak in the area)

Thus, tomato flu remains a diagnosis of exclusion until specific molecular diagnostic tools are developed.[27]

6. Importance of Early Diagnosis

Early diagnosis helps:

- ✓ Prevent unnecessary use of antibiotics.
- ✓ Reduce the spread of infection among children.
- ✓ Enable proper isolation and symptomatic management.
- ✓ Avoid misdiagnosis as dengue or chikungunya.

7. Preventive Diagnostic Measures

Public health departments recommend:

- ✓ Regular monitoring of viral outbreaks
- ✓ Screening in schools and childcare centers
- ✓ Maintaining record of symptomatic cases
- ✓ Using rapid viral test kits to rule out similar diseases.[28]

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

Fig no. 4: Blisters in Tomato Flu-affected patient (A–hand, B–face and body, C–foot, D–mouth)[29]

6. PREVENTION

1. Isolation of Infected Individuals

- Children infected with tomato flu should be isolated for 5–7 days after symptom onset.

- Prevents the spread of infection to classmates, family members, and the community.

2. Personal Hygiene

- Wash hands frequently with soap and clean water.
- Avoid touching eyes, mouth, and nose unnecessarily.
- Maintain short and clean fingernails to reduce infection spread.[30]

3. Avoid Sharing Personal Items

- Do not share utensils, clothes, towels, bedding, or toys with infected persons.
- Contaminated objects can transmit the virus easily among children.

4. Disinfection of Surroundings

- Regularly clean and disinfect surfaces and commonly touched items (door handles, toys, tables).
- Use disinfectants like sodium hypochlorite solution (household bleach).[31]

5. Adequate Hydration and Nutrition

- Ensure the patient drinks plenty of fluids (water, fruit juice, ORS) to prevent dehydration.
- Provide soft, nutritious food to maintain energy and immunity.

6. Avoid Scratching Blisters

- Scratching can lead to secondary bacterial infection and delayed healing.
- Keep the skin clean and use mild antiseptic lotions if recommended by a doctor.[32]

7. Symptomatic Treatment

- Give paracetamol or acetaminophen for fever and body ache as per doctor's advice.
- Avoid unnecessary use of antibiotics since the disease is viral in nature.

8. School and Public Awareness

- Schools should educate parents and teachers about early symptoms and preventive steps.
- Encourage reporting and early isolation of suspected cases.[33]

9. Use of Masks and Respiratory Hygiene

- Infected or symptomatic children should use a mask while coughing or sneezing.
- Dispose of tissues properly and wash hands after coughing or sneezing.

10. Government and Community Measures

- Public health authorities should monitor outbreaks, provide rapid testing, and spread awareness through media and posters.
- Encourage routine surveillance in childcare centers.[34]

7. TREATMENT

- Tomato flu (Tomato fever) is a self-limiting viral infection mostly affecting young children.
- There is no specific antiviral medicine or vaccine available yet.
- Hence, treatment focuses on symptomatic relief, boosting immunity, and preventing complications.
- Three major systems of medicine — Ayurveda, Homeopathy, and Allopathy — offer supportive care.[35]

1. ALLOPATHIC TREATMENT

Table No .1: Allopathic Treatment Of Tomato Flu.

Sr. No.	Drug Name (Generic)	Category / Use	Dose & Duration	Purpose / Effect
1	Paracetamol (Acetaminophen)	Antipyretic / Analgesic	10–15 mg/kg every 6–8 hours for 3–5 days	Reduces fever, headache, and body pain
2	Ibuprofen	NSAID (Pain reliever, anti-inflammatory)	5–10 mg/kg every 8 hours as needed (for 3–5 days)	Reduces pain, swelling, and inflammation
3	Cetirizine / Chlorpheniramine	Antihistamine	Once daily for 5–7 days	Relieves itching and allergic skin irritation
4	Calamine Lotion / Zinc Oxide Ointment	Topical skin soothing agent	Apply twice daily until blisters heal (5–10 days)	Reduces irritation, dryness, and promotes healing of blisters
5	Lidocaine Oral Gel	Local anaesthetic (topical)	Apply on mouth ulcers 2–3 times a day before meals	Reduces pain in mouth ulcers and helps eating comfortably
6	ORS (Oral Rehydration Solution)	Electrolyte fluid	As needed (sips throughout the day)	Prevents dehydration due to fever and poor intake
7	Coconut Water / Fruit Juices / Fluids	Supportive	Frequent small intakes during illness	Maintain hydration and energy levels
8	Mupirocin Ointment	For secondary	Apply thin layer 2–3	Prevents or treats

	(Topical Antibiotic)	skin infection	times/day for 5–7 days	bacterial infection in blisters
9	Amoxicillin–Clavulanate (if infection present)	Broad-spectrum antibiotic	40–45 mg/kg/day in divided doses for 5–7 days (doctor's advice only)	Treats secondary bacterial infection
10	Vitamin C & Multivitamin Syrup	Nutritional supplement	Once daily for 10 days	Supports immune function and recovery

2. AYURVEDIC TREATMENT

➢ **Some advantages of tomato flu**

- Ayurvedic treatment helps in natural recovery from Tomato Flu by improving body immunity and reducing symptoms like fever, rashes, and tiredness.
- Herbs such as Tulsi, Giloy, Neem, and Ashwagandha help the body fight infection and remove toxins.
- Ayurveda focuses on balancing the three doshas (Vata, Pitta, Kapha) and supports faster skin healing.
- It is safe, chemical-free, and suitable for children, providing relief without side effects. Along with herbal medicines, Ayurveda also promotes healthy diet, rest, and cleanliness, which help in complete recovery and prevention of future infections.

➢ **Some herbs useful in tomato flu**

1. tulsi
2. ashwagandha
3. harida (turmeric)
4. amla (indian goosbery)
5. giloy (guduchi)

1. Tulsi

- **synonyms:** holy basil, sacred basil
- **family:** lamiaceae (Mint family)
- **Biological Source:** Tulsi consists of the fresh or dried leaves and flowering tops of Ocimum sanctum Linn. (syn. Ocimum tenuiflorum Linn.)
- **Chemical Constituents:** Eugenol, Ursolic acid, Linalool, Carvacrol.

- **Uses**

- Beneficial for stress relief and improving immunity
- Promotes oral and digestive health

2. Ashwagandha

- **Synonyms:** Withania somnifera (L.) Dunal, Indian ginseng
- **Family:** Solanaceae
- **Biological Source:** Dried roots and leaves of Withania somnifera (L.) Dunal
- **Chemical Constituents:** Withanolides, Alkaloids (somniferine, withanine), Sitoindosides, Steroidal lactones, Flavonoids

- **Uses**

- reduces stress, anxiety, and fatigue
- Improves strength, stamina, and immunity

3. Amla (Indian Gooseberry)

- **Synonyms:** Indian Gooseberry
- **Family:** Phyllanthaceae (formerly Euphorbiaceae)
- **Biological Source:** Fresh or dried fruits of Phyllanthus emblica (syn. Emblica officinalis Gaertn.)
- **Chemical Constituents:** Ascorbic acid (Vitamin C), Tannins (emblicanin A & B, punigluconin, pedunculagin), Polyphenols, Gallic acid, ellagic acid, Flavonoids.
- **Uses**

- Potent antioxidant and rejuvenator (Rasayana)
- Improves digestion and liver function

4. Giloy (Guduchi)

- **Synonyms:** Guduchi, Amrita
- **Family:** Menispermaceae
- **Biological Source:** Stems (and sometimes roots and leaves) of Tinospora, cordifolia (Willd.) Miers
- **Chemical Constituents:** Alkaloids (berberine, tinosporine, magnoflorine), Glycosides (tinosporaside), Diterpenoid lactones (tinosporon, cordifolide), Steroids and polysaccharides, Phenolic compounds
- **Uses**

- Effective in fever, diabetes, and liver disorders
- Enhances vitality and general immunity

2. HOMEOPHATHIC TREATMENT

1. Arsenicum

- **Synonyms:** Arsenicum album, White arsenic
- **Family:** Mineral origin
- **Biological Source:** Prepared from arsenious oxide (As_2O_3) — a mineral compound purified and triturated for medicinal use
- **Chemical Constituents:** Arsenious oxide (As_2O_3), Contains trace impurities of arsenates or arsenites depending on source
- **Uses**

- In homeopathy, used for anxiety, digestive disorders, food poisoning, skin diseases, and respiratory ailments
- Exhibits antiseptic and tonic properties in minute doses.

- **Source:** Mineral (arsenic trioxide).

- **Extraction Process**

- The raw arsenic trioxide is first ground with lactose (milk sugar) in the ratio of 1:99 to make the 1X triturated powder.
- Further triturations (up to 3X) are made, then dissolved in alcohol–water mixture for liquid potencies.

- **Potentization:** By serial dilution and succussion (e.g., 6C, 30C, 200C).

2. Rhus toxicodendron

- **Synonyms:** Rhus tox, Poison Ivy
- **Family:** Anacardiaceae
- **Biological Source:** Prepared from the fresh leaves of Toxicodendron radicans (formerly Rhus toxicodendron), a North American shrub.
- **Chemical Constituents:** Urushiol, resins, tannins, and volatile oils

- **Uses**

- In homeopathy, Rhus tox 30C is widely used for:
- Rheumatic and arthritic pains (worse at rest, better with movement and warmth)

- **Source:** Fresh leaves of the poison ivy plant.
- **Extraction Process**

- The fresh leaves are harvested and macerated in alcohol (usually 90–95% ethanol).
- Kept for 8–14 days with occasional shaking.
- The mixture is filtered to obtain the mother tincture (Q).

- **Potentization:** The mother tincture is then diluted and succussed to required potencies.

3. belladona

- **Synonyms:** Atropa belladonna Linn, Deadly Nightshade
- **Family:** Solanaceae
- **Biological Source**

- Dried leaves and flowering tops of Atropa belladonna Linn.
- The roots are also sometimes used for medicinal preparations.

- **Chemical Constituents:** Tropane alkaloids: Atropine, Hyoscyamine, Scopolamine (Hyoscine), Flavonoids, Coumarins, Volatile bases

- **Uses**

- Headache, sore throat, and tonsillitis

- Inflammation of eyes, ears, and skin

➢ **Source:** Fresh whole plant (especially leaves and roots) collected before flowering.

➢ **Extraction Process**

- The plant is finely chopped and macerated with strong alcohol (95% ethanol).
- The mixture is left for a few days and then filtered to obtain the mother tincture.

➢ **Potentization:** The mother tincture is further diluted and succussed to form higher potencies (e.g., 6C, 30C).

4. Gelsemium perfoliatum

➢ **Synonyms:** Yellow Jasmine, Carolina Jessamine

➢ **Family:** Loganiaceae

➢ **Biological Source**

- Prepared from the fresh root of Gelsemium sempervirens (syn. Gelsemium perfoliatum)
- The mother tincture is made in alcohol, then diluted and potentized to 30C in homeopathy.

➢ **Chemical Constituents**

Alkaloids : 1. Gelsemine, Gelseminine, Gelsemicine

2. Gelsemoidine

3. Essential oil and resins

➢ **Uses**

- Flu-like conditions with weakness, drowsiness, and lack of energy
- Headache starting from the neck and spreading to the forehead

➢ **Source:** Fresh root of the yellow jasmine plant.

➢ **Extraction Process**

- The fresh root is cleaned, crushed, and macerated with alcohol (about 90% ethanol).

- After 8–10 days, it is filtered to prepare the mother tincture (Gelsemium Q).

➢ **Potentization:** Done by serial dilution and succussion.

5. Eupatorium perfoliatum

➢ **Synonyms:** Eupatorium perfoliatum Linn.

➢ **Common names:** Boneset, Thoroughwort, Agnimony

➢ **Family:** Asteraceae (Compositae)

➢ **Biological Source**

- Prepared from the fresh leaves and flowering tops of Eupatorium perfoliatum Linn.
- The mother tincture is made using alcohol, then potentized to 30C for homeopathic use.

➢ **Chemical Constituents:** Volatile oil , Bitter glycosides (eupatorin, eupatrin) Tannins, Sesquiterpene lactones, Flavonoids and resins

➢ **Uses**

- Fever with severe bone and muscle pain (“as if bones are broken”) common in dengue, malaria, and influenza
- Promotes sweating and helps relieve fever naturally

➢ **Source:** Fresh leaves and flowering tops of the plant (boneset).

➢ **Extraction Process**

- The plant material is crushed and macerated with alcohol.
- The mixture is allowed to stand for about 10–14 days and then filtered.
- The filtrate forms the mother tincture (Eupatorium perfoliatum Q).

➢ **Potentization:** Diluted and succussed to obtain desired potencies.

8. ADVANCEMENTS OF TOMATO FLU

1. LIVE ATTENUATED VACCINES (LAVS)

- **LAV** development depends on finding highly attenuated and genetically stable strains.
- Wang et al. engineered **CVA6-G64S** and **CVA6-G64T** mutants (mutation at 3Dpol G64).
- These strains showed reduced pathogenicity and higher replication fidelity than wild type.
- Provides theoretical basis for **CVA6 LAVs**, but no immunogenicity testing was done.
- Future need: discover more attenuated strains + test safety & immune response.

2. VIRUS-LIKE PARTICLE (VLP)

- Vaccines **VLPs** mimic real virus structure but contain no genetic material, so safe & highly immunogenic.
- **CVA6 VLPs** successfully expressed in bacterial, yeast, insect (B/IC), and CHO cell systems.
- Studies lack comparison of yield and quality across these systems.
- A kinetic model using CHO-cell **VLP** production helps understand **VLP** release & process optimization.
- Major limitations:
- Low mechanical stability of **CVA6 VLPs.**
- Presence of RNA fragments, increasing slight infectious potential.
- Needs improvement in **VLP** stability & safety.

3. SUBUNIT VACCINES

- Made from purified antigenic protein fragments + adjuvant.
- Deng et al. designed a multivalent epitope-based vaccine **(EV-A71, CVA16, CVA10, CVA6, CVB3)**.
- Computer-predicted conserved B-cell, HTL, CTL epitopes linked to rpIL adjuvant.
- Produced in E. coli but antibody response was:
- Good for **EV-A71 & CVB3**
- Poor for **CVA6 & CVA10** (minimal/no neutralization)
- No animal protection studies done.
- Problems: low cross-reactivity, protein folding issues in E. coli.
- More research needed on epitope structure & B-cell responses.

4. DNA VACCINES

- Contain genes encoding viral antigens to induce long-lasting immunity.
- Safe (no live virus/RNA).
- Bello et al. created VP1me **DNA** vaccine containing epitopes from **EV-A71, CVA16, CVA10, CVA6.**
- Expressed well in HEK293A cells and induced strong IgG + CD8 T-cell responses in mice.
- But neutralizing ability against **CVA6** not tested.
- Current data on **CVA6 DNA** vaccines is limited; needs more detailed in vivo safety & efficacy studies.

5. mRNA VACCINES

- Injected **mRNA** instructs cells to produce viral antigens → fast immune activation.
- Advantages: safe, rapid production, strong immunity.
- First **CVA6 mRNA** vaccine study (China):
- Constructed P1/VP1 **mRNA** with UTRs, tPA signal, polyA tail.
- Compared **VLP vs mRNA** (LPP-mRNA) vaccines.
- **VLP** → strong neutralizing antibodies + T-cell response.
- **mRNA** → strong T-cell response + cross-protection against **CVA10**.
- Suggests combining humoral + cellular immunity may create next-gen vaccines.
- Advances in Lipid Nanoparticles (LNPs) improve **mRNA** stability & delivery.

6. MULTIVALENT VACCINES

- Include **CVA6** along with **CVA10, CVA16, EV-A71** (inactivated, **VLP,** subunit, **DNA** types).
- Challenge: different antigens show different immunogenicity, causing imbalanced immune response.
- Antigenic interference can reduce neutralizing antibody output.
- Tetravalent VLP studies show:
- Good compatibility among antigens.
- CVA6, CVA10, CVA16 show lower immunogenicity than EV-A71 → may require higher antigen dose.

- Immune interference may result from competition for T-cell help (Tfh cells) and B-cell activation.
- Optimizing antigen ratios is essential for balanced immunity.

9. DISCUSSION

Tomato flu is an emerging illness reported mainly in India, particularly among children below five years of age. Current evidence strongly suggests that Tomato flu is not a completely new virus but an atypical presentation of **Hand, Foot and Mouth Disease (HFMD)** caused by **Coxsackievirus A16** or **Enterovirus-71.**[37] The characteristic red, tomato-like blisters, along with fever, fatigue, and body pain, make the condition clinically significant, although it remains self-limiting in most cases.[38]

A major challenge is the absence of a **specific diagnostic test**, making it necessary to rule out other viral infections such as dengue, chikungunya, Zika, chickenpox, and classical HFMD. This creates confusion in clinical practice, especially during seasonal outbreaks of viral fevers.[39]

Treatment across all medical systems—Allopathy, Ayurveda, and Homeopathy—focuses on **symptomatic management**, as no antiviral medicine or vaccine is yet available. Preventive measures such as isolation, hygiene practices, and environmental disinfection are essential to control transmission, especially in schools and childcare settings.[40]

Recent advancements in vaccine research, including **VLP, DNA, and mRNA vaccines**, show promising immune responses, but more studies and clinical trials are required before a safe and effective vaccine becomes available.[41]

Overall, Tomato flu is mild but highly contagious, highlighting the need for early diagnosis, proper isolation, public awareness, and continued research to strengthen preparedness for future outbreaks.[42]

10. CONCLUSION

Tomato flu is a mild viral illness that mostly affects small children, but it can spread quickly in communities when proper care is not taken. Even though it first appeared like a new disease, research now shows that it is closely linked to Hand, Foot and Mouth Disease,

caused mainly by Coxsackie viruses. The symptoms such as fever, red blisters, tiredness, and irritation can be uncomfortable, but most children recover on their own within a week.

Because there is no special test or specific medicine for Tomato flu, doctors focus on treating the symptoms and preventing dehydration or secondary infections. Simple steps like isolating infected children, maintaining cleanliness, and avoiding shared items play an important role in stopping the spread. Ongoing research on different types of vaccines is encouraging, but more studies are needed before a safe vaccine becomes available.

Overall, Tomato flu reminds us that hygiene, awareness, and early care are the best tools to manage viral infections in children. With proper precautions and supportive treatment, the disease can be controlled effectively and safely.

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