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Conference report

Establishment of Asia-Pacific Network for Enterovirus Surveillance

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ABSTRACT

Enteroviruses (EV), the major pathogens of hand, foot, and mouth disease (HFMD) and herpangina, affect millions of children each year. Most human enteroviruses cause self-limited infections except polioviruses, enterovirus A71 (EV-A71), enterovirus D68 (EV-D68), and several echoviruses (Echo) and coxsackieviruses (CV). Especially, EV-A71 has repeatedly caused large-scale outbreaks in the Asia-Pacific region since 1997. Some Asian countries have experienced cyclical outbreaks of severe EV-A71 infections and initiated development of EV-A71 vaccines. Five EV-A71 vaccine candidates have been clinically evaluated and three of them were approved for marketing in China. However, none of the China-approved products seek marketing approval in other countries.

This situation supports a role for collaboration among Asian countries to facilitate clinical trials and licensure of EV-A71 vaccines. Additionally, enterovirus D68 outbreaks have been reported in the US and Taiwan currently and caused severe complications and deaths. Hence, an Asia-Pacific Network for Enterovirus Surveillance (APNES) has been established to estimate disease burden, understand virus evolution, and facilitate vaccine development through harmonizing laboratory diagnosis and data collection. Founded in 2017, the APNES is comprised of internationally recognized experts in the field of enterovirus in Asian countries working to raise awareness of this potentially fatal and debilitating disease. This article demonstrated the summaries of the first expert meeting, 2017 International Workshop on Enterovirus Surveillance and Vaccine Development, held by APNES in Taipei, Taiwan, March 2017.

1. Introduction

Enteroviruses (EV), the major pathogens of hand, foot, and mouth disease (HFMD) and herpangina, affect millions of people each year worldwide, especially among infants and young children [1–3]. The genus ***Enterovirus*** belongs to the family *Picornaviridae* and consists of 13 species, including four species causing human infections (*Enterovirus* species A ~ D). Human EV could be classified into more than 100 serotypes. Most human enteroviruses cause self-limited infections except polioviruses, enterovirus A71 (EV-A71), enterovirus D68 (EV-D68), and several echoviruses (Echo) and coxsackieviruses (CV) which could result into neurological complications. Especially, EV-A71 has repeatedly caused large-scale outbreaks of severe HFMD in the Asia-Pacific region since 1997 [4]. The rapid progression of severe complications, such as central nervous system disease and cardiopulmonary failure, can lead to death within 24 to 48 hours [5]. The overall household transmission rate of EV-A71 was 52%, and particularly high at 84% among children under 6 years of age [6]. Patients with uncomplicated EV illness bring significant economic and medical impacts on society with at least 1–4 days of missed school or lost work, and direct medical costs of $69–771 USD per case and indirect costs of $63–422 USD per case mainly attributable to parental missed work [7].

EV-A71, one of the EV-A viruses, is the major etiologic agent of HFMD and herpangina. Based on phylogenetic analysis of VP1 genes, EV-A71 viruses are divided into 8 genogroups A to H

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[8–10]. Genogroup A comprises the prototype EV-A71 strain (BrCr-CA-70), which was isolated in 1970 in the United States [11]. Genogroup B and C can be further divided into major genotypes B1-B5 and C1-C5, respectively. Recently, genogroups D and G were identified in India [12], genogroups E and F were identified in Africa, and genogroup H was identified in Pakistan [8–10]. Genogroup B and C have been causing large-scale epidemics in Asia since 1997, particularly B4, B5, C2, C4 and C5 genotypes are often associated with severe outcomes of large-scale EV-A71 epidemics in Asia and the Pacific region [13–15]. The genogroups B4, B5, and C4 are mainly restricted to Asian countries while C1 and C2 circulate mainly in Europe [16,17]. However, EV-A71 B5 has been reported in France [18] and Denmark [19]. B0 genotype was retrospectively identified in the Netherlands [20]. Distribution of EV-A71 genotypes within and outside the Asia-Pacific region from 1963 to 2014 are shown in Figs. 1 and 2 respectively [4,16,19–31].

Since 1997, large-scale epidemics of severe EV-A71 infections have been sequentially reported in Malaysia (1997), Taiwan (1998), Singapore (2000), Vietnam (2005), Brunei (2006), China (2007), and Cambodia (2012). Interestingly, EV-A71 strains circulating in these countries are highly related, which showing that genotype C4 and B5 viruses are endemic in China and Southern Asia, respectively, and spread to other countries in this area (Fig. 3). Some of these countries have experienced cyclical outbreaks of severe EV-A71 infections and initiated development of EV-A71 vaccines as a public health priority. Currently, three EV-A71 vaccines have been licensed in China but none of them has been qualified by the World Health Organization (WHO) or the European Union (EU) for international distribution [32]. Longitudinal surveillance data are critical for design of clinical trials and formulation of vaccination policy [20,33]. Although the WHO Western Pacific Regional Office (WPRO) has established a HFMD reporting system since 2011, the system is hampered by some limitations. First, the data format related to disease severity is not consistent. Second, the online biweekly report does not include laboratory diagnosis and EV serotyping. Overall, the HFMD reporting system is not optimal to understand the epidemiology of different circulating EV serotypes [34,35]. Therefore, a laboratory-based enterovirus surveillance network is urgently needed and would be more useful to monitor the disease burdens of different circulating EV serotypes, especially in Asian countries experiencing large-scale epidemics of EV-A71 infections [20].

To overcome the limitations of the current HFMD reporting system, the Asia-Pacific Network for Enterovirus Surveillance (APNES) was established through collaborations between academic institutions and hospitals in Cambodia, Malaysia, Vietnam and Taiwan in 2017, with the aims of establishing harmonized laboratory diagnosis and estimating disease burdens of different enterovirus serotypes to accelerate development of EV-A71 vaccines in these countries. Founded in 2017, APNES comprised of internationally recognized experts in the field of enterovirus in Asian countries working to raise awareness of the potentially fatal and debilitating disease. The APNES held its first expert meeting, 2017 International Workshop on Enterovirus Surveillance and Vaccine Development, in Taipei, Taiwan, March 2017. This conference focused on the significant increases in enterovirus incidence in Asian countries where the disease is endemic and in areas most affected by the disease.

2. Laboratory diagnosis

Laboratory diagnosis is critical to differentiate EV serotyping and genotyping. There are several methods for laboratory diagnosis of enterovirus infections, including virological, molecular, and serological methods. Virological methods include virus isolation and immunofluorescence assay (IFA). Molecular methods include reverse transcription-polymerase chain reaction (RT-PCR) targeting 5′ untranslated region (5′UTR), real-time RT-PCR targeting VP1 gene, and consensus-degenerate hybrid oligonucleotide primers (CODEHOP) RT-PCR targeting VP1 gene (VP1-CODEHOP)

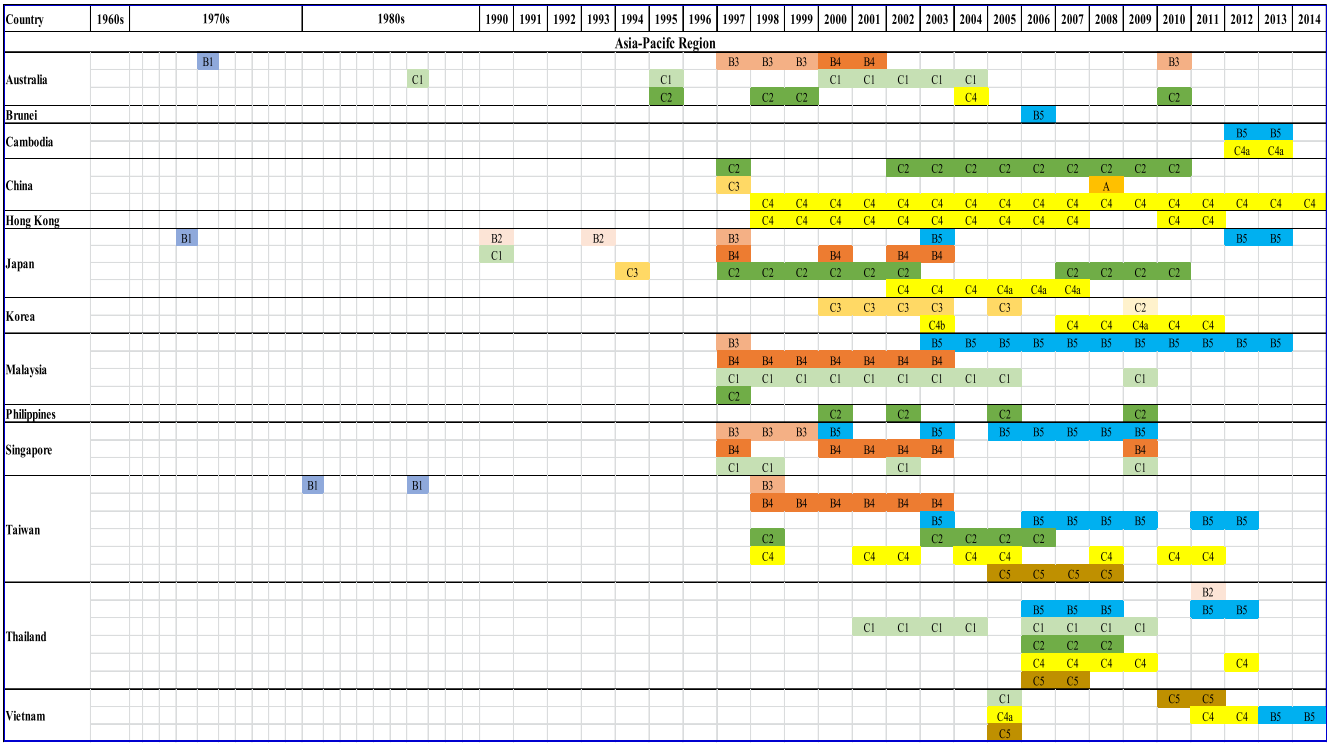

Fig. 1. Distribution of EV-A71 genotypes in the Asia-Pacific region from 1963 to 2014.

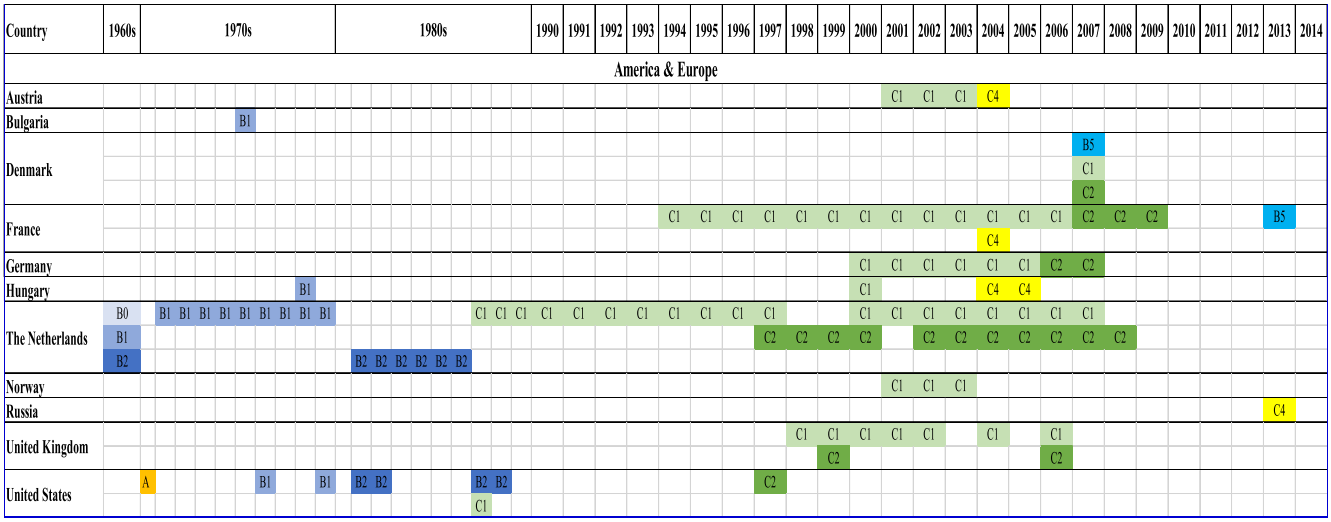

Fig. 2. Distribution of EV-A71 genotypes in America and Europe from 1963 to 2014.

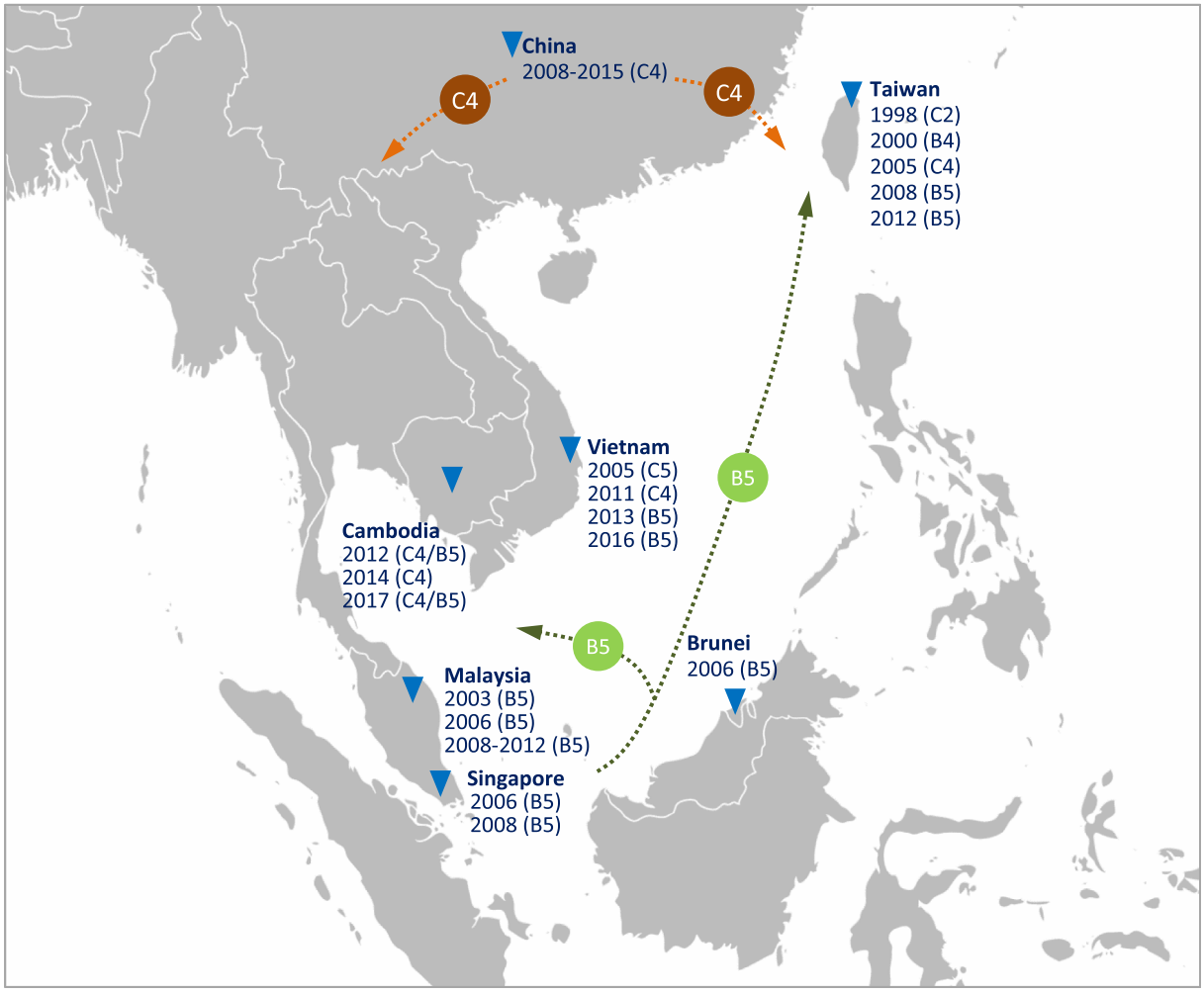

Fig. 3. International Spreading of EV-A71 in the Asia-Pacific Region. Map adapted from https://upload.wikimedia.org/wikipedia/commons/4/4d/BlankMap-World.svg.

[36–44]. Serological methods include neutralization assay and enzyme-linked immunosorbent assay (ELISA) immunoglobulin M (IgM). The advantages and disadvantages of laboratory diagnosis methods for Enterovirus infections are listed in Table 1. Overall, the real-time RT-PCR is the popular method for rapid diagnosis of EV-A71 infections, but it can only detect one or two serotypes of EV in one reaction [16]. In a direct comparison, the VP1-CODEHOP performed better than virus isolation and 5′UTR

Table 1
Laboratory diagnosis methods for determing serotypes of Enterovirus infections.

Methods	*Advantages*	*Disadvantages*
Virus Isolation/ IFA	Provide virus isolates for further study	Low sensitivity, Time consuming (~7 days), Multiple monoclonal antibodies required
Real-Time RT-PCR	High sensitivity, Rapid test within 4 hours	Multiple primers for different genotypes, High cost
5′UTR RT-PCR	High sensitivity, Time-saving (2–3 days)	Labor intensive, False positivity, Multiple primers for different genotypes, Sequencing required
VP1 CODEHOP RT-PCR	High sensitivity and specificity, Time-saving (2–3 days), PCR product can be used for sequencing and genotyping	Labor intensive, Sequencing required
Neutralizing Assay	High sensitivity and specificity	Time consuming due to requiring paired sera, Labor intensive, Live virus required
ELISA serum IgM	Rapid test within 4 hours	1. False positivity due to cross-reactivity 2. Low positivity in the first 2 days of disease onset
Chromatography serum IgM	Rapid test within 1 hour	1. False positivity due to cross-reactivity with other EV 2. Low positivity in the first 2 days of disease onset

IFA = immunofluorescence assay; RT-PCR = reverse transcription polymerase chain reaction; CODEHOP = consensus degenerate hybrid oligonucleotide primer; ELISA = enzyme-linked immunosorbent assay.

RT-PCR for detection of enterovirus infections using throat swabs. In addition, the VP1-CODEHOP could be a better method for virus surveillance because it can concurrently detect multiple EV serotypes [15]. Moreover, the VP1-CODEHOP was recommended in the WHO poliovirus surveillance guideline in 2015 [45]. Typical enterovirus surveillance studies usually involves virus isolation which requires multiple cell lines and good specimen quality and transportation to increase sensitivity. At the moment, laboratory-based enterovirus surveillance systems have not been harmonized. Based on experiences from the laboratory-based global influenza surveillance, harmonization is critical to the success of international surveillance (http://www.who.int/influenza/gisrs_laboratory/en/). After considering cost and effectiveness, we propose a work-flow guideline for laboratory-based enterovirus surveillance investigation (Fig. 4). To reduce costs, it would be desirable to first conduct the VP1-CODEHOP PCR. After obtaining the serotype and genotype information through the VP1-CODEHOP PCR, throat swabs from patients infected with unique serotypes and genotypes could be selected for virus culture which could be further used for genome sequencing using the next generation sequencing (NGS) and antigenic analysis using serological assays. Recently, NGS technology has been applied for virus genomic studies and identifying novel enteroviruses [46–49]. Moreover, the NGS could identify coinfections of enteroviruses, which are common in children but could not be easily differentiated using virus isolation and traditional molecular assays [47]. However, the NGS is time-consuming and is still too expensive as a first-line diagnosis tool [47]. Therefore, the APNES proposes to use the CODEHOP as the first-line diagnosis tool and select unique samples for genome sequencing using NGS. Several clinical specimens including throat swabs, stools and cerebrospinal fluid (CSF) could be used to detect enteroviruses. CSF could only be available from severe cases with neurological complications and the other specimens could be easily obtained from mild cases. Previous studies have shown that throat swabs are the most sensitive clinical specimens for isolation of EV-A71 [50–52]. Moreover, enterovirus could be detected in stools of HFMD patients more than one month, which indicates that stools are the ideal specimens for laboratory diagnosis of acute enterovirus infections. Overall, throat swabs are the most suitable clinical specimens for enterovirus surveillance. However, clinical specimens may not be available in resource-limited areas or under special situations. If this is the case, sewage samples could be used to detect enteroviruses, which is recommended tool for global poliovirus eradication [53]. Harmonized standard operation procedures will be developed and released in the APNES website for reference.

3. Enterovirus surveillance system

In order to monitor and control EV-A71 or HFMD outbreaks, several surveillance systems at community or national levels have been implemented in epidemic countries in the Asia-Pacific region, [54] including China, [5] Japan, [55] Korea, [56] Malaysia, [57] Singapore, [58] Thailand, [59–60] Taiwan [15,61] and Vietnam, [62] as well as other countries outside the Asia-Pacific region, including Denmark, [63] Germany, [64] Greece, [3] Spain, [16] Switzerland [65], the United States, [1] and the European Union [66,67].

To the best of our knowledge, Japan started the earliest HFMD surveillance in 1983 compared to other Asian countries [55]. This is followed by the Korea Centers for Disease Control and Prevention (KCDC) National Enterovirus Surveillance System which has monitored EV infections in 180 clinics since 1993 [56]. Malaysia also commenced surveillance for HFMD and herpangina after the huge outbreak in Sarawak and the Malaysian Peninsula in 1997 [57]. In Taiwan, a national EV surveillance system was established by Taiwan Centers for Disease Control (Taiwan CDC) after EV-A71 epidemic occurred in 1998 [15,24]. Singapore initiated a clinical surveillance system in April 1998 for identification of HFMD within child-care centers during a HFMD epidemic to formulate a preparedness response to monitor and manage severe HFMD outbreaks. As a result of this, Singapore was well prepared to manage its largest known HFMD outbreak at the end of 2000 [58]. Vietnam reported its first case of HFMD in 2003, and its national surveillance data showed that the number of cases and deaths due to HFMD increased dramatically year by year from 2007 to 2009, with a peak in 2011 [62]. After large outbreaks of HFMD in multiple provinces in 2008, the Chinese government established a national enhanced surveillance system in May 2008. From the national surveillance system of HFMD in China, they found the risk of cardiopulmonary or neurological complications was 1·1%, and the case-fatality rate was 0·03%. Furthermore, the severe-case fatality risk was 3·0%, with over 90% of deaths associated with EV-A71 [2,5].

Outside the Asia-Pacific region, USA reported data collected from the National Enterovirus Surveillance System (NESS) at the Centers for Disease Control and Prevention (CDC) during 1983–2003. However, NESS is not a population-based surveillance system [1]. Germany initiated the National Reference Centre for Poliomyelitis and Enteroviruses in 2005 [64]. In Greece, a supplementary laboratory surveillance of enteroviruses was implemented in 2008 [3]. In Switzerland, an EV surveillance study was conducted between January 2013 and December 2015 [65]. In Denmark, an enhanced non-polio EV pilot surveillance system was

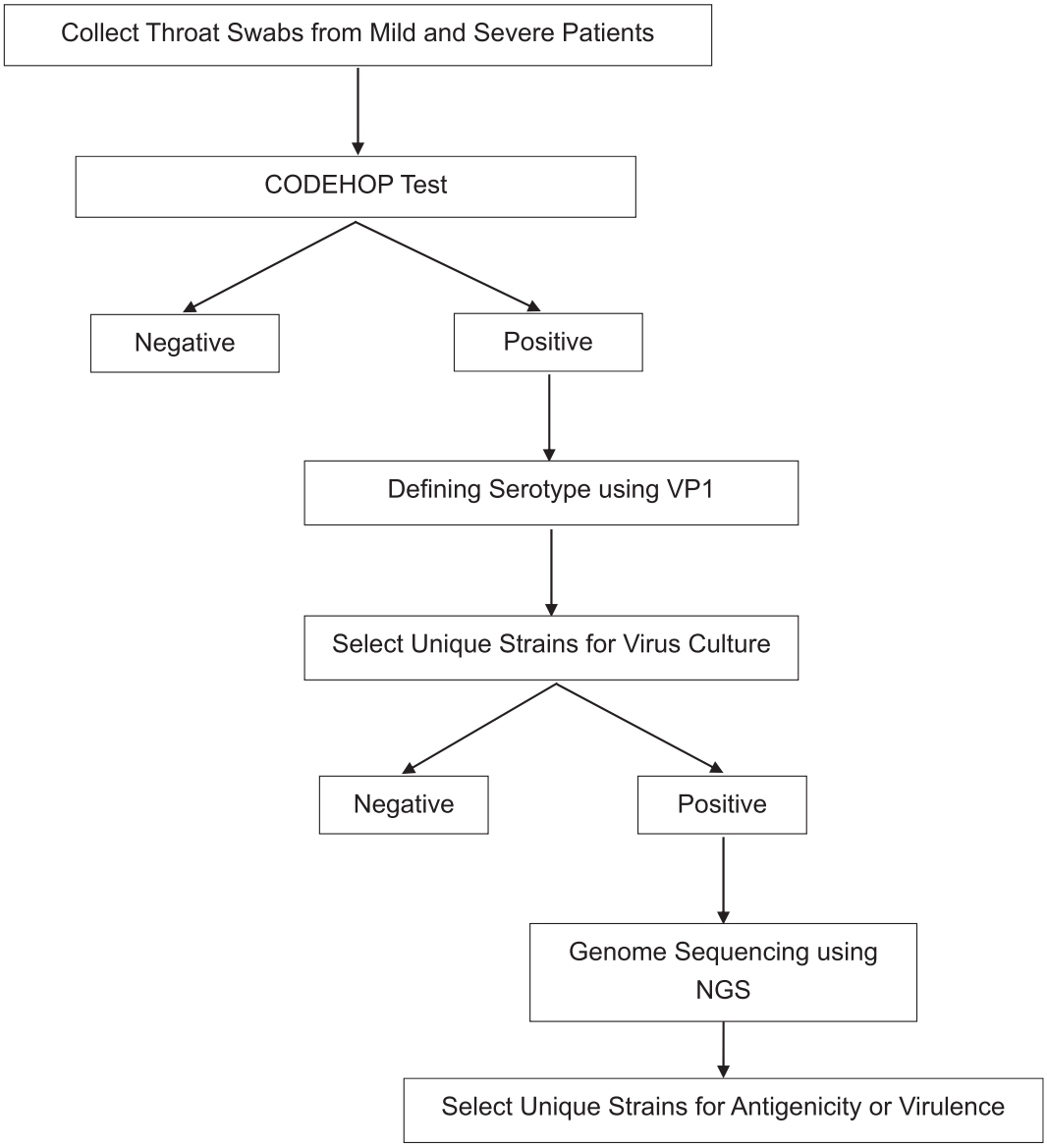

Fig. 4. Study Flowchart of Asia-Pacific Network for Enterovirus Surveillance. Abbreviations: HFMD = Hand, Foot, and Mouth Disease; CODEHOP = Consensus-Degenerate Hybrid Oligonucleotide Primer; NGS = Next Generation Sequencing.

established in September 2014 [63]. Spain implemented HFMD and Enterovirus surveillance in 2016 [16]. Recently, the European Non-Polio Enterovirus Network (ENPEN) has been established in the EU to improve EV diagnostics, collate data on severe EV infections and monitor the circulation of EV types [66,67]. Overall, only Japan and Taiwan have established national laboratory-based enterovirus surveillance systems which provide monthly enterovirus serotyping information in public domain [68,69]. This effort would be useful for regional EV surveillance and should be expanded to other Asia-Pacific countries with high risk of EV-A71 outbreaks.

By 2017, about 10 Asian countries had reported large-scale EV-A71 outbreaks. Among them, development of EV-A71 vaccines has been initiated in China, Malaysia, Singapore, Taiwan and Vietnam but only three vaccine candidates were approved for marketing in China [70]. Current production capacity of EV-A71 vaccines in China is unable to meet the domestic demand and as such, Chinese vaccine manufacturers are not planning to obtain marketing approval in other countries. Therefore, it is desirable for other Asian countries to collaborate through the establishment of the Asia-Pacific Network for Enterovirus Surveillance (APNES) to share essential epidemiological data to eventually initiate plans for EV vaccine development. The APNES was established in 2017 by six academic and medical institutions in Cambodia, Malaysia, Taiwan, and Vietnam since these four countries have reported large-scale EV-A71 epidemics and have larger birth cohorts for initiating efficacy trials of EV vaccines (Table 2). The objective of APNES is to set up a scientific platform to share knowledge and experience, through information exchange and consultation, on epidemiology, virology, and risk management of Enterovirus, particularly in the Asia-Pacific region. The members of APNES include the Institut Pasteur du Cambodge (IPC) in Cambodia, University of Malaya (UM) and University Malaysia Sarawak (UNIMAS) in Malaysia, the Children's Hospital No. 1 of Ho Chi Minh City (CH1-HCMC) and the Pasteur Institute of Ho Chi Minh City (PI-HCMC) in Vietnam, and the National Health Research Institutes (NHRI) in Taiwan. Table 2 provides some available information of severe neurological cases related to enterovirus 71 epidemics in Asia since 1997.

Table 2
Severe neurological cases related to enterovirus 71 epidemics in Asia since 1997.

Country (No. of newborn*)	Year	No. of severe cases ‡ (death)	No. tested (lab methods)	No. of EV71-confirmed cases (death)
Cambodia (367,000) [31]	2012–2013	170 (98)	170 (qRT-PCR)	116 (81)
	2014	122 (N/A)	122 (qRT-PCR)	97 (N/A)
	2015	30 (N/A)	30 (qRT-PCR)	7 (N/A)
	2016	16 (N/A)	16 (qRT-PCR)	2 (N/A)
Sarawak, Malaysia (509,000†)	1997	281	N/A	N/A (0)
	2000	461	286 (RT-PCR)	91 (1)
	2003	244	231 (RT-PCR)	102 (2)
	2005	201	80 (RT-PCR)	0 (0)
	2006	794	536 (RT-PCR)	86 (6)
	2008	506	11 (RT-PCR)	9 (2)
	2009	687	58 (RT-PCR)	13 (0)
	2012	331	209 (RT-PCR)	18 (0)
Taiwan (198,000) [69,78–79]	1998	405 (78)	96 (IFA)	78 (34)
	2000	291 (41)	291 (IFA. RT-PCR)	151 (25)
	2001	393 (58)	393 (IFA. RT-PCR)	182 (27)
	2002	162 (30)	162 (IFA. RT-PCR)	57
	2005	142 (16)	142 (IFA, qRT-PCR)	82 (8)
	2008	373 (14)	373 (IgM, qRT-PCR)	346 (14)
	2012	153 (2)	153 (IgM, qRT-PCR)	139 (1)
	2016	33 (1)	33 (IgM, qRT-PCR)	23 (1)
Southern Vietnam (1,547,000 †)	2011	1547	1152 (RT-PCR)	1129
	2012	2528	749 (RT-PCR)	728
	2013	1420	489 (RT-PCR)	484
	2014	850	262 (RT-PCR)	224
	2015	609	80 (RT-PCR)	63
	2016	442	70 (RT-PCR)	64

N/A: Not available.
* Average number of newborns per year from 2011 to 2015.
† Newborn data is based on national data.
‡ Definition of severe case: Cambodia- cardiopulmonary failure (CPF) or central nervous system (CNS) involvement; Taiwan- severe CNS involvement or CPF; Malaysia- severe neurological complications or systemic disease; Vietnam-myoclonus, autonomic dysfunction with fever that is not responsive to antipyretics and with hypertension and persistent tachycardia, cardiopulmonary compromise with pulmonary edema or hemorrhage [80].

4. EV-A71 vaccine development

EV-A71 or multivalent vaccines against enteroviruses is urgently required to prevent repeatedly severe HFMD outbreaks in some Asian countries. In response to the Bulgaria epidemic in 1975, an inactivated EV-A71 whole virus vaccine candidate was produced in Moscow and evaluated in Bulgaria in 1976. This EV-A71 vaccine candidate was well tolerated and immunogenic in children 1–4 years of age. However, for the practical reason of having no further outbreaks of EV-A71, the Bulgaria vaccine candidate was not further evaluated for its clinical efficacy [22,57]. Due to large outbreaks of EV-A71 in Asia since 1997 and the absence of effective treatment, the development of efficacious EV-A71 vaccines has been a national priority in several Asian countries. Five inactivated EV-A71 vaccine candidates have been developed in Taiwan, Singapore, and China and evaluated in Phase 1–3 clinical trials (Table 3) [4,20,22].

In Taiwan, the Taiwan CDC and Taiwan NHRI developed a genotype B4-based EV-A71 vaccine and launched the first human Phase I clinical trial in adults in 2010. A single vaccine dose of 5 μg or

Table 3
Formalin-Inactivated EV71 vaccine candidates in human clinical trials.

Organizations	Cell Line	EV71 Strain	Dosage (μg)	Population Target	Sample Size	Status	References	Technology Transfer
Sinovac Biotech Co., Ltd (China)	Vero cell	C4a (H07 strain)	1	6–35 month children	10,077	marketing approved in China	NCT01507857	
Beijing Vigoo Biological Co., Ltd. (China)	Vero cell	C4a (FY7VP5 strain)	0.8	6–35 month children	10,245	marketing approved in China	NCT01508247	Wuhan Institute of Biological Products Co., Ltd.
CAMS (China)	KMB-17 cell	C4a (FY-23 K-B strain)	0.25	6–71 month children	12,000	marketing approved in China	NCT01569581	
NHRI (Taiwan)	Vero cell	B4	5 and 10	20–43 year adults	60	Phase 1 completed	NTC01268787	Enimmune Corp.; Medigen Vaccine Biologics Corp.
Enimmune Co. (Taiwan)	Vero cell	B4	0.25, 0.5, 1, 2 and 5	6 month –6 year children	122	Phase 2 completed	NCT02777411	
Medigen Vaccine Biologics Co. (Taiwan)	Vero cell	B4	150	2 month – 12 year children	366	Phase 2 completed	NCT02200237	
Inviragen (Singapore)	Vero cell	B2	0.6 and 3	Adults	36	Phase 1 completed	NCT01376479	

Abbreviations: CAMS = Chinese Academy of Medical Sciences; NHRI = National Health Research Institute.

10 μg was safe and highly immunogenic [71]. It elicited 100% seroconversion in naive volunteers and strong virus neutralizing antibody (VNA) responses (geometric mean titer [GMT] = 210) against the vaccine strain as well as against the B1, B5, and C4a strains in 85% of the vaccines [72]. In contrast, neutralizing response against C4b and an atypical C2 viruses were low but these two EV71 genotypes are not currently circulating [20]. The genotype B4 candidate has been transferred to two local companies in Taiwan for clinical development targeting young infants, which have finished phase II studies and are planning phase III studies.

In Singapore, Inviragen (Takeda Pharmaceuticals Co Ltd) conducted a Phase I trial in adults with an EV71 genotype B2 vaccine. All subjects who received 0.6 μg or 3 μg of vaccine at days 0 and 28 seroconverted and developed VNA GMTs of 323 and 452, respectively [20,24,73].

In China, three EV-A71 vaccine candidates were developed by Beijing Vigoo Biological Co., Ltd, Sinovac Biotech Co., Ltd., and the Institute of Medical Biology at the Chinese Academy of Medical Sciences (CAMS). Beijing Vigoo Biological Co., Ltd transferred the technology of EV-A71 vaccine to Wuhan Institute of Biological Products Co., Ltd. in 2011. These three vaccine candidates in China are all inactivated whole-virus alum-adjuvant vaccines that use C4 genotype virus as the vaccine strain and target infants and children over 6 months of age [4]. Based on the results of Phase III clinical trials of EV-A71 vaccines in China, the safety of the EV-A71 vaccine is satisfactory in infants and children and can provide more than 90% protection against EV-A71-associated HFMD and 80% of EV-A71-associated disease [20]. China FDA approved these three EV-A71 vaccines during 2015–2017. The approved EV-A71 vaccines are now in commercial production in China [4,74]. Nonetheless, the certified Chinese vaccines are currently not pre-qualified by WHO and have not obtained marketing approval outside China [16]. Moreover, despite the clinical efficacy of EV-A71 vaccines in China, they could not provide cross-protection across other Enterovirus species such as CA2, CA6, CA10 and CA16, the main agents responsible for HFMD outbreaks through the Western Pacific Region [20,23,74,75]. Therefore, a combined multivalent vaccine that can provide protection against various enterovirus serotypes and can be applied worldwide is important for enterovirus prevention.

An international network for enterovirus surveillance and clinical trials is urgently needed to help design and conduct efficacy trials in epidemic countries. The establishment of APNES was for the following reasons. First, infants are the target population of EV vaccines and multi-nation randomized controlled trials are required to prove clinical protection in this age group. Second, longitudinal prospective cohort studies are warranted to clarify clinical and epidemiological significances of the antigenic and genetic variations, which are critical to the selection of vaccine strains [22,71]. Third, an ideal EV vaccine should be inexpensive, safe, compatible with large-scale production, easy to administer, and acceptable to parents. Therefore, harmonization and standardization of vaccine strain, quality control reagents and immunoassays, and animal models at the international level is demanded to evaluate the potency of vaccine candidates and determine which manufacturing process yields the most effective and most affordable products [20].

5. Conclusion

EV-A71, the major cause of fatal HFMD outbreaks, causes cyclical epidemics in several Asian countries [4]. In addition to EV-A71, other novel enteroviruses such as newer strains of CV-A2, CV-A10, ECHO11 and EV-D68, are increasingly becoming emerging threats [76,77]. Therefore, it is desirable to establish a laboratory-based enterovirus surveillance system in Asian countries experiencing cyclical enterovirus epidemics. In this respect, we propose the Asia-Pacific Network for Enterovirus Surveillance (APNES) as a platform for international regional collaboration to monitor EV evolution and to accelerate vaccine development.

Contributions

MLC contributed to the design, article analysis and drafted the manuscript. MSL provided critical review and revision, and supervised the findings of this work. STL, YYC, WYC, TN and HKT verified the analytical findings and provided comments. VD, PD, YFC, DP, MHO conducted data collection for the epidemics table, provided critical review and commentary on the manuscript. All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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