identical. These results suggest that the genetic sequence of the *B.anthracis* strains were conserved; and no genetic differences associated with the geographical distribution and time of six strains. Among them, however, three strains were isolated from the patients who didn't contact with infected animal. In such cases, this leads to the question what is the real source of the infection. Environmental sample such as soil can be important source and route of anthrax infection in Vietnam. However, the PCR result was based on the experimental stage because the spores were created from *B.anthracis* strain. Up to now, there is still lacking evidence of isolated *B.anthracis* strain from soil samples in Vietnam. In this study, moreover, the number of *B.anthracis* strains was very limited. To clearly determine the molecular epidemiology of Anthrax in Vietnam a number of *B.anthracis* isolates should be increased and isolated from different sources.

Another result of the present study is the Anthrax network has successful created in Vietnam, especially in the high risk areas in the North of Vietnam. We have the anthrax teams in the preventive medicine center in the provinces and others in the communes. They are available to contact by the hot line and/or cell phone and make a monthly report of anthrax to NIHE.

Conclusion:

A rapid and direct *B.anthracis* - PCR has a good performance in both clinical and environmental samples in Vietnam. Concurrently, an Anthrax network has also created in Vietnam, especially in the high risk areas. In the study, the genetic sequence of the six VN-*B.anthracis* isolates were conserved; and no genetic differences associated with the geographical distribution and time of these strains. There is still need to isolate *B.athracis* from environment, human and animals in order to determine a main source of the disease in Vietnam.

Recommendation:

It is necessary to find out a link between animal – human- environment by using modern molecular methods. Further molecular epidemiological studies need to be done to establish etiology of *B.anthracis* and initiate strategies to implement anthrax control measure in Vietnam.

Re-training for the local medical staff on Anthrax disease should be frequently conducted.

Research 7: ***Enhancement of NIHE rabies laboratory capacity for rabies/bat lyssavirus diagnosis and research***

ABSTRACT

Background: Rabies has been a serious public health problem in Vietnam. Annually, approximately 100 fatal human cases of rabies are reported, the majority attributable to canine rabies. The problem is that by now, in Vietnam the rabies surveillance system has focused merely on clinical report, not confirmed by laboratory tests. To assess the effectiveness of program for rabies control and prevention, it is necessary to base on the evidence of laboratory. We therefore strengthen NIHE rabies laboratory capacity for rabies/ *lyssavirus* diagnosis and research to support for elimination of rabies by 2020 as call for action of ASEAN +3 countries.

Methods: The quick, easier and effective techniques for rabies diagnosis such as RT – LAMP, FAVN, and ELISA or advanced techniques for research (transformation, transfection and protein expression) were developed in NIID and transferred to NIHE laboratory by on side trainings. Then, the evaluation and application of developed techniques were implemented in NIHE by using clinical samples. The quality assurance of NIHE laboratory was implemented by NIHE - NIID inter-laboratory testing or by EQA program supported by NIID. FAVN technique was used for performing research on bat lyssaviruses in Northern provinces with financial support of WHO, Vietnam country office.

Results: NIHE laboratory can perform standard techniques for rabies laboratory testing, and has abilities to furnish EQA program for antigen and genome detection to other laboratories. Under this technical support, we conducted research on molecular of rabies virus, the results showed that rabies viruses in Vietnam belong to genotype 1 and were further divided into 2 main groups. Group1 was distributed in the whole country whereas group 2 was only found in the Northern part of the country and shared high similarity with viruses isolated in the South of China. A survey for bat *lyssaviruses* in Northern Vietnam was concurrently implemented and showed that the overall presence of neutralizing antibodies against *lyssaviruses* of bat population in this study was 193/789 (24.4%). With this finding and NIID – NIHE collaboration work, two scientific papers were established and two others were submitted to national/ international peer review journals. In addition, two laboratory researchers successfully defended their Master of Science theses based on this collaboration and research.

Conclusion: technical capacity of NIHE rabies laboratory was strengthened and had abilities to perform rabies diagnosis and research to support for rabies control and prevention program.

Recommendation: continue getting technical and biological material supports of NIID to perform collaborative research and diagnosis support for rabies control and prevention program.

Research 8: Phylogenetic analysis and transmission dynamics of measles and rubella viruses isolated from some outbreaks in the Northern provinces of Vietnam from 2006 to 2014

ABSTRACT

Background: The measles vaccine was introduced into the immunization program in 1981 in Vietnam. A series of different measles vaccination strategies were implemented at different stages of measles control. The rubella vaccine was not introduced. This study investigated the genotype distribution of MV in Vietnam from 2006 -2014 to establish a genetic baseline before MV elimination in Western Pacific Region (WPR). Continuous and extensive measles virus surveillance and the ability to quickly identify imported cases of measles will become more critical as measles elimination goals are achieved in Vietnam in the near future. This is report that a single endemic genotype of measles virus has been found to be continuously circulating in the north Vietnam for at least 8 years and the first step discribe 2B genotype of rubella virus circulation in the northern provinces.
Methods: Isolate measles/rubella virus using Vero/SLAM cell line. RT PCR to detect RNA of Measles and Rubella virus from MV isolates and throat swab. Genotyping rubella and measles viruses based on 739 nucleotide of E1 gene region and 450 nucleotide of N gene region, respectively.

Results: The results showed that all of the strains of MV to genotype H1. There are 6 MV isolates in 2006, 17 MV in 2008, 26 MV in 2009, 25 sequences of MV in 2010, 3 sequences in 2011 and 26 sequences in 2013. The nucleotide sequence homologies of the 103 H1 strains were 97.8%–100%. The phylogenetic tree of RV is shown that all of the strains of RV belonged to genotype 2B. There are 2 RV isolates in 2008, 12 RV in 2009 and 32 RV in 2011. The nt difference between the Vietnamese strains in 2008-2009 ranged from 0.1% to 1.3%. The nt difference between the Vietnamese in 2011 strains ranged from 0.8% to 1.4%. The nucleotide sequence homologies of the 46 2B RV strains were 96.2%–100%.

Conclusion: Genetic analysis results showed that the H1 genotype of measles virus and 2B genotype of rubella virus was the predominant endemic measles virus in the North VietNam in 2006-2013.

Research 9: Laboratory diagnosis of enteroviruses from cases with hand, foot, and mouth disease and molecular characteristics of EV71 strains isolated in Vietnam North in 2011-2012

ABSTRACT
1046/1642 clinical samples from patients with hand, foot and mouth disease in 2011-2012 collected from Northern provinces of Vietnam are positive with enteroviruses including 534 positive samples with HEV71 (51%) and 268 positive samples with Coxsackievirus A6 (25.6%) and 166 as Coxsackievirus A16 (15.8%); 6% as other CoxsackieA viruses including CA type 3, 10, 12 and 13, Coxsackievirus type B, echo viruses, Polio-Sabin virus and enteroviruse typ 96. 15 samples were identified as Rhinovirus (1.4%). Phylogenetic analysis of 135 HEV71 strains showed 2 genogroups B and C with 3 subgenogroups as B5, C4 and C5 that cocirculated in norththern Vietnam in 2011-2012. However, predominated subgenogroup of HEV71 are belonging to subgenogroup C4 with 63.6%, after subgenogroup C4 is B5 with 30.3 %, and only 6.1% as subgenogroup C5 that circulated during a long period before. HFMD outbreak appeared in 28/28 provinces in the **North of Vietnam and** was mainly detected in children under 3 years of age
Keywords: Hand, Foot and Mouth Disease, enterovirus, human enterovirus 71, coxsackie virus A6, A16; coxsackie virusB5; Echo virus30

- **Methods:**

Specimen Collection
A total of 1642 specimens were collected from the children with HFMD. Each child had at least 1 specimen collected from vesicle fluid, throat swab, or stool. 20% of specimens in PBS (+) were treateded with chloroform (1:10 in phosphate-buffered saline) before use for virus isolation in cell culture or molecular biology
Table1, Primer used for research

AN32	5-GTYTGCCA	cDNA	3009-3002	
AN33	5-GAYTGCCA		3009-3002	
AN34	5-CCRTCRTA		3111-3104	
AN35	5-RCTYTGCCA		3009-3002	
SO224-F	5-GCIATGYTIGGIACICAYRT	PCR1	2207-2226	762
SO222R	5-CICCIGGIGGIAYRWACAT		2969-2951	
AN89F	*5-CCAGCACTGACAGCA*GYNGARAYNGG	*PCR2/EVs*	2602-2627	375
AN88R	*5-TACTGGACCACCTGG*NGGNAYRWACAT		2977-2951	
MAS01S	5'-ATAATAGCA(C/T)T(A/G)GCGGCAGCCCA-	*PCR2/EV71*	2352-2375	376

	3'			
MAS02 A	5' – AGAGGGAG(A/G)TCTATCTC(C/T)CC -3'		2709-2728	
2349F	5'–GCYTAYATAATAGCAYTGGCGGCAGC-3'	*PCR& Seq/EV71*		
3393R	3'–CACCCGTTGAADTCYCACCARTTGGCGG-5'			
2757F	5'– GCHAAYTGGGAYATAGACATAAC-3'	*SeqEV71*		
2780R	3'– CCCTRTATCTGTATTGDCC-5'	*SeqEV71*		

RNA extraction, Stool suspensions were prepared by adding 5 ml of phosphate-buffered saline (+), 1 g of glass beads (Corning Inc,, Corning, NY), and 0,5 ml of chloroform to 1 g of stool sample, shaking the mixture vigorously for 20 min in a mechanical shaker, and centrifuging at 1,500 _ *g* for 20 min at 4°C (33), the supernatant was transferred to a fresh tube, (10% stool suspensions),
140 _l of the specimen extract was combined with an equal volume of
Vertrel XF (Miller-Stephenson Chemical Co,, Danbury, CT), shaken vigorously, and then centrifuged at 13,000 _ *g* for 1 min at room temperature, The aqueous phase was transferred to a fresh tube, Other specimen types (including blister fluid; throat swab samples) were processed without pretreatment, Twenty micrograms of proteinase K (Roche Applied Science, Indianapolis, IN) was added to 140 _l of each liquid specimen or fecal extract, and the mixture was then incubated for 30 min at 37°C, Nucleic acid was extracted from the digested specimen with a QIAamp Viral RNA mini kit (QIAGEN, Inc,, Valencia, CA), which was used according to the manufacturer's instructions, The eluted RNAs were passively dried in a benchtop desiccator under vacuum, The dried RNA was resuspended in 16 _l of sterile nuclease-free water and stored at _20°C until use,

RT-snPCR and sequencing.
- Synthesis of cDNA was carried out in a 5 µl reaction mixture containing 4 µl of RNA and 1 pmol each cDNA primer (primers AN32, AN33, AN34, and AN35; Table 1), heat mix in a 70^0C hear block for 5 min and immediately chill in ice water for at least 5 min.
In a 20 µl reaction mixture containing 05 µl RNA reaction mixture, 100 µM each deoxynucleoside triphosphate (dNTP; Invitrogen), 4 µl of 5 x reaction buffer (GoStript, Promega), 1.5 µl MgC12, 20 U of RNasin (Promega Corp,, Madison, WI), and 100 U of GoScript reverse transcriptase (Rocke) , incubation at 25°C for 05 min, 42°C for 60 min, and 70°C for 15 min
- Synthesis of PCR1: Following incubation, the entire 05 µl RT reaction mixture was then used in the first PCR (final volume, 25 µl) (PCR1), consisting of 5 µl of 10 x PCR buffer (Roche Applied Science), 200 µM each dNTP, 50 pmol each of primers 224 and 222 (Table 1), and 2,5 U of *Taq* DNA polymerase (Roche Applied Science), with 40 cycles of amplification (95°C for 30 s, 42°C for 30 s, 60°C for 45 s),
One microliter of the first PCR was added to a second PCR (PCR2/EV71) for seminested amplification, PCR2/EV71 contained 40 pmol each of primers MAS01S and MAS02A (Table 1), 200 µM each dNTP, 5 µl of 10 x FastStart *Taq* buffer (Roche Applied Science), and 2,5 U of FastStart *Taq* DNA polymerase (Roche Applied Science) in a final volume of

50 µl, The FastStart *Taq* polymerase was activated by incubation at 95°C for 6 min prior to 40 amplification cycles of 95°C for 30 s, 60°C for 20 s, and 72°C for 15 s, The reaction products were separated and visualized on 2% agarose gels containing 0,5 µg ethidium bromide per ml

One microliter of the first PCR was added to a second PCR (PCR2/EV) for seminested amplification, PCR2 contained 40 pmol each of primers AN89 and AN88 (Table 1), 200 µM each dNTP, 5 µl of 10 x FastStart *Taq* buffer (Roche Applied Science), and 2,5 U of FastStart *Taq* DNA polymerase (Roche Applied Science) in a final volume of 50 µl, The FastStart *Taq* polymerase was activated by incubation at 95°C for 6 min prior to 40 amplification cycles of 95°C for 30 s, 60°C for 20 s, and 72°C for 15 s, The reaction products were separated and visualized on 1,2% agarose gels containing 0,5 µg ethidium bromide per ml and were purified from the gel by using a QIAquick gel extraction kit (QIAGEN), Slight variations in the sizes of the PCR products (350 to 400 bp) were observed due to VP1 gene length differences in the different serotypes, as described previously (12–14, 19), The resulting DNA templates were sequenced with a BigDye Terminator v1,1 ready reaction cycle sequencing kit on an ABI Prism 3100 automated sequencer (both from Applied Biosystems, Foster City, CA) by using primers AN89 and AN88 (Table 1)

RT-PCR/sequencing: Viral RNA was extracted from 200 µl of culture supernatants with High Pure Viral RNA kit (Roche Diagnostics GmbH, Mannheim, Germany). RT-PCR was performed with Accesss RT-PCR System (Promega Co., USA) using 2µl of each viral RNA and 10 pmol of the 2349F (sense: 5'–GCYTAYATAATAGCAYTGGCGGCAGC-3', Y = C or T) and the 3393R (antisense: 3'–CACCCGTTGAADTCYCACCARTTGGCGG-5') primers. Each reaction mixture was incubated in a thermal cycler by the following steps: 45 min at 48°C, 2 min at 94°C, 35 cycles of 94°C for 10 sec, 50°C for 10 sec, 65°C for 1min and then at 65°C for 5 min. Amplification of the fragments was confirmed by 1% agarose gel electrophoresis and the amplicons were purified with a Wizard SV gel and PCR clean up System (Promega). The entire VP1 genome of the purified amplicons was determined for both strands with oligonucleotide primers using an ABI 3100 genetic analyzer. The sequencing primers were, the 2349F, 2757F (sense: 5'– GCHAAYTGGGAYATAGACATAAC-3', H=A or T or C, Y=C or T), 2780R (antisense : 3'– CCCTRTATCTGTATTGDCC-5' R=A or G, D=A or G), and 3393R. The sequence chromatograms were assembled with the Sequencher software. Multiple sequence alignments were performed with the Clustal W program and phylogenetic analysis was carried out using the neighbor-joining method with 1000 times bootstrap replications. The phylogram tree was drawn with the TreeView program, using the reference strains of EV71 as an outgroup.

Sequence analysis:

✓ Confirmation of EV71 and other enterovirus : by electropholysis and detect specific PCR products

✓ Confirmation of enterovirus serotypes and EV71 genogroup by sequencing:

- Confirmation of enterovirus serotypes: Trim the data using Sequencer 4.2.2 program and NCBI nucleotide - nucleotide BLAST. The amplicon sequences were compared with the VP1 sequences of EV reference strains, including at least one representative of each recognized serotype, by script-driven sequential pair wise comparison with the program

Gap (Wisconsin Sequence Analysis Package, version 10,2; Accelrys, Inc,, San Diego, CA), as described previously (15, 18, 19), In cases where the result was not unequivocal (highest score less than 75% or second-highest score greater than 70%), the deduced amino acid sequences were compared by a similar method.

- Confirmation of EV71 genogroup by Mega-5 program

- **Results:**

1. Enteroviruses was protected by snRT-PCR and Seq.

Table1. Result of Enteroviruses and EV71 by snRT-PCR in 2011-2012

Year	N collected samples	N (+)	% (+)	n (+) EVs	(+) EV71		(+) Enterovirus	
					N(+)	%(+)	N(+)	%(+)
2011	912	603	63.5	588	275	45.6	313	54.4
2012	730	443	60.6	443	252	57	191	43
TT	1642	1046	62%	1031	527	51%	504	49%

In 2011-2012, 1046 of 1642 HFMD cases (63.7%) were found positive for HEV by using enterovirus general primers and snRT-PCR method. HEV-71 and EVs occupied 51% (527) and 49% (504) respectively.

Table2. Result of enterovirus serotypes by sequencing in 2011-2012

HEV71	Result of Enterovirus serotypes by seq.						
	(+) Coxsackievirus - A			(+) CB	(+) Echo	(+) Other EV	Rhinovirus
	CAV- 6	CAV-16	Other CAV				
527 51%	268 25.6 %	166 15.8%	34 3.0%	5	28	3 (EV96 & Polio)	15
	44.6%			3.0%			1.4%

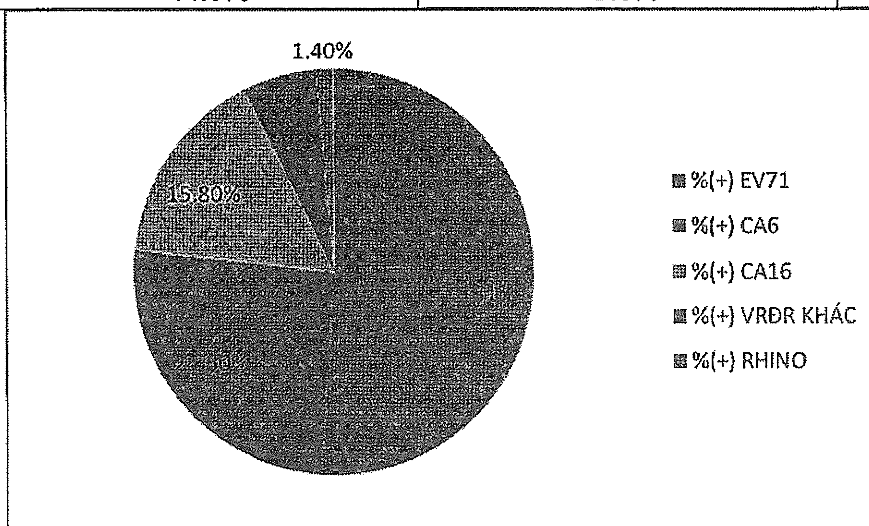


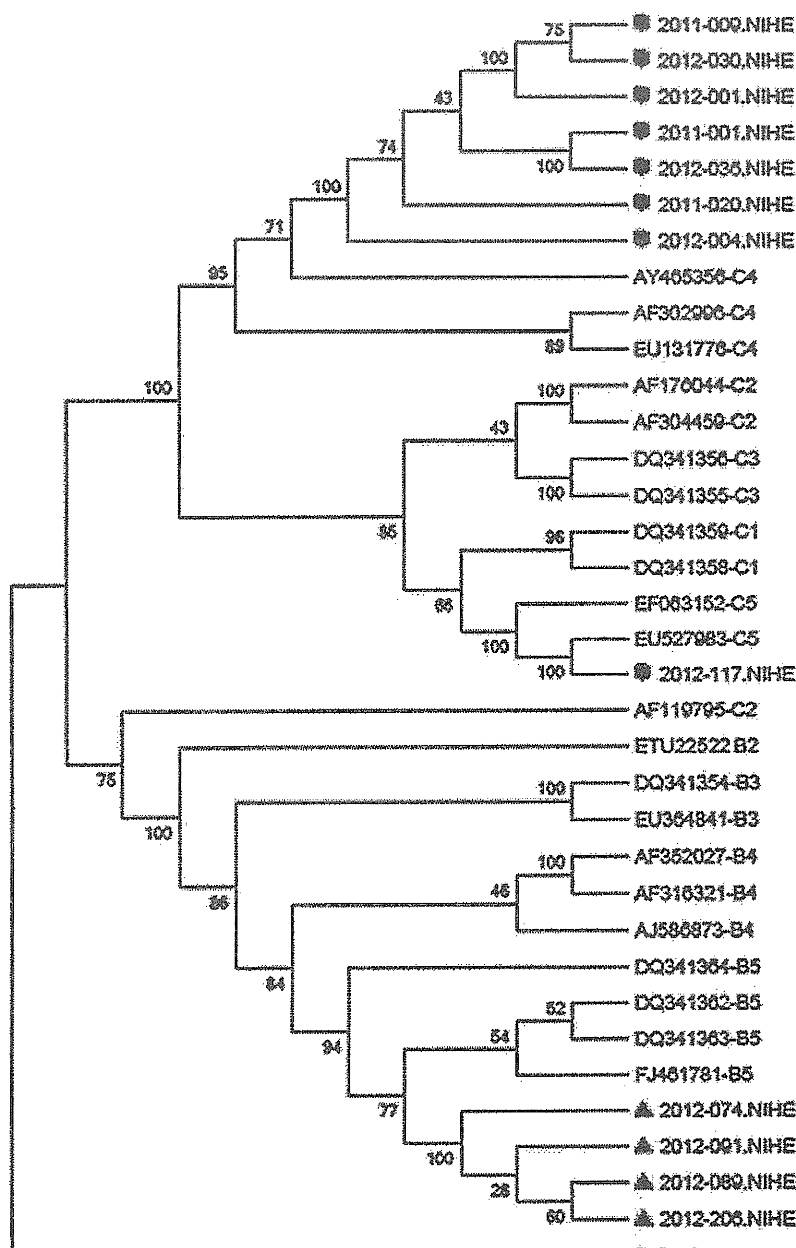
Figure1. Percentage of EV71 and other EVs in HFMD outbreak in 2011-2012

519 of other EVs PCR-2 products were sequenced with primer pairs at position of primer F 2602-2627 or primer R 2977-2951 (375nt). The result showed with 25.6% of CoxsackieA 6; 15.8% of CoxsackieA16. The other entroviruses containing 6.0% with CV-A3(2), A10(4), A12 (10), và A13 (4); CV-B3, B4 (5); 28 echovirus type 30 and 2 Polio, 1 EV96 were also detect.

Table 3. Enterovirus type 71's subgenogroups detected in 2011-2012

TT of PCR produts/EV71	TT of EV71 PCR products sequenced	C4	C5	B5
527	135	86	8	41
% of each EV71 subgenogroup		63.7%	6.0%	30.3 %

135 PCR products of EV71 were amplified and sequenced. Result showed 63.7% as subgenogroup C4, 6.0% as subgenogroup C5 and 30.3 % as subgenogroup B5



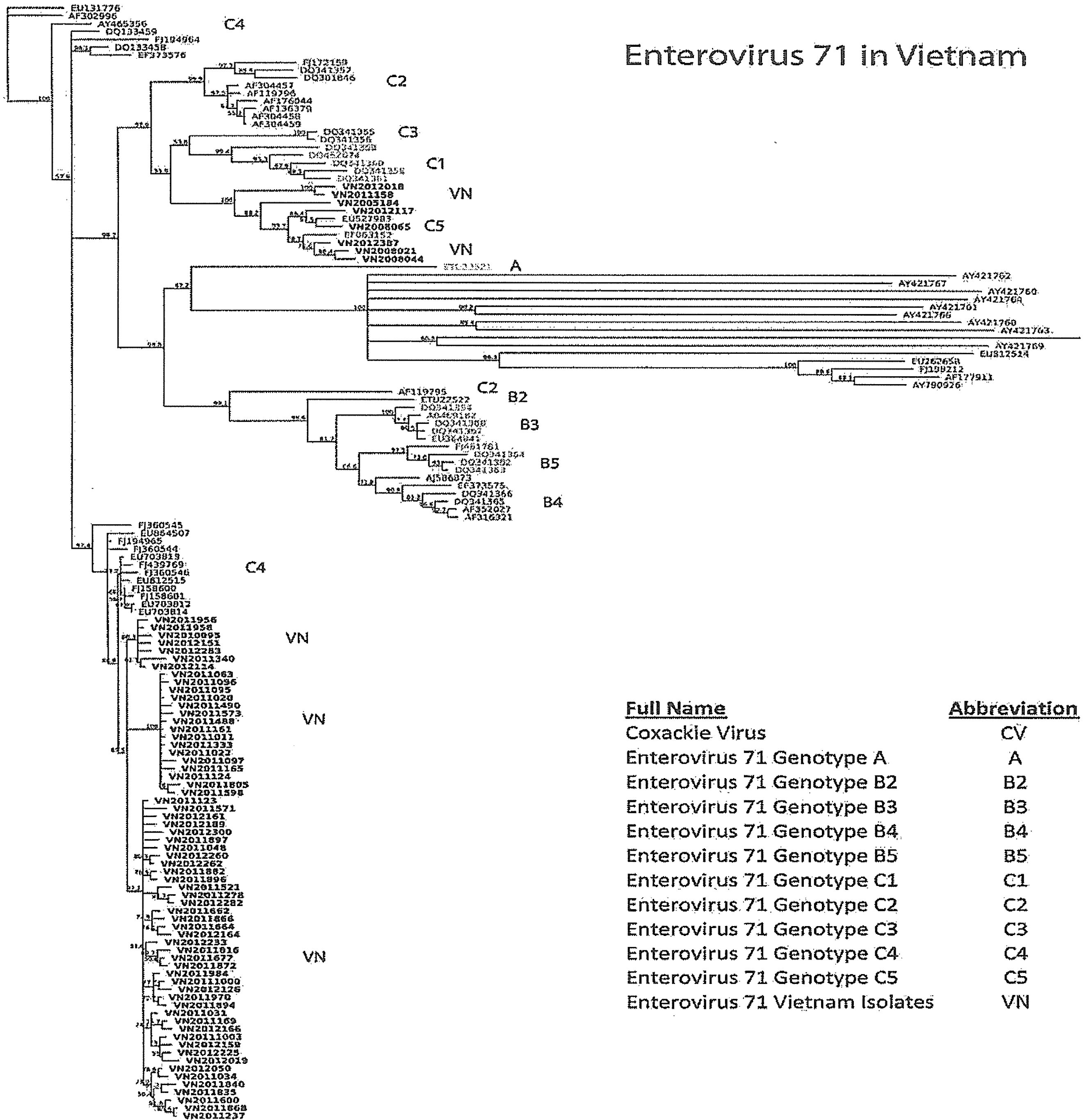


Figure 2. Phylogenetic relationships of human enterovirus 71 (HEV71) strains belonging to genogroup B and C in 2011-2012

35 HEV71 strains and 100 PCR2 products/HEV71 were sequenced. Result showed 2 genogroups containing genogroup B and genogroup C. Genogroup C with 63.6% of subgenogroup C4 predominantly responsible for almost all HEV-71 infections in 2011-2012 in the north of VN and 6.0% of subgenogroup C5, and 30.3% belonging to genogroupB with subgenogroup B5. However, the analysis of recent and previous HEV71

isolates in the Western Pacific Region showed that several subgenogroups as B1, B2, B3, B4, C1, C2, C3 and C4 were cocirculating in Australia, Malaysia, Singapore, Taiwan and Japan respectively.

CONCLUSION

1. Hand, foot and mouth disease outbreak in 2011-2012 was caused by enteroviruses. HEV-71 is the main cause, accounting for 51% and 49% of other enteroviruses;
In total of EVs confirmed in 2011-2012: 51 % of HEV-71, 25.6% of CAV-6, 15.8% was CAV-16 and the rest was other EVs
2. Enterovirus typ71 contained two genogroups (genogroup B and C) with 3 subgenogroups containing 63.7% as subgenogroup C4, 6.0% as subgenogroup C5 and 30.3 % as subgenogroup B5
3. Mainly age of disease was children within 3 years, there was no difference of the incidence caused HFMD by enterovirus type 71 (51%) and other enteroviruses (49%) in each age group.
4. The disease occurred in all provinces of Vietnam north (delta and mountainous areas) with co-circulation and caused HFMD of HEV-71 and CAV-6 and 16

Recommendation:

1. Confirmation subgenogroups of pending EV71-PCR2 products in 2011-2013: 278 of pending PCR2 products
2. Confirmation serotypes of pending PCR2 products of EVs in 2011-2013: 76 of pending PCR2 products
3. Confirmation subgenogroups of PCR2 products of EV71 and serotypes of PCR2 products of EVs in 2014-2016 in the North of Viet Nam
4. Confirmation subgenogroups of PCR2 products of EV71 and serotypes of PCR2 products of EVs, and Epidemiology research of HFMD in 2014-2016 in Hai Phong City
5. EV71 strains Analysis to examine evolution of EV71 strains during 2003-2016

平成２５年度業績

＊研究成果の刊行に関する一覧表

＊学会発表一覧表

研究成果の刊行に関する一覧表　(平成２５年度)

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