



HOKKAIDO UNIVERSITY

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Activities of WHO Collaborating Centre for Zoonoses Control

Hokkaido University Research Center for Zoonosis Control



Established in 2005

Hiroshi Kida, DVM, PhD, MJA

University Professor, Hokkaido University

Head, Specially Invited Professor, Research Center for Zoonosis Control

Head, OIE Reference Laboratory for Avian Influenza

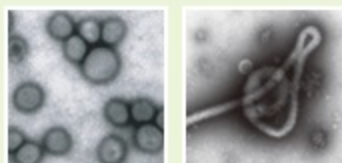
Head, WHO Collaborating Centre for Zoonoses Control

**Head, National Research Center for the Control and Prevention of Infectious Diseases,
Nagasaki University**

Research Center for Zoonosis Control, Hokkaido University

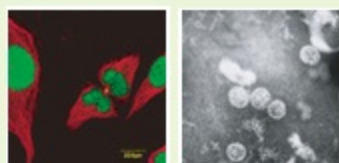
Division of Global Epidemiology

- Identification of natural host animals and transmission routes of zoonotic pathogens
- Genetic analysis of pathogens
- Epidemiological research
- Global surveillance of zoonoses



Division of Molecular Pathobiology

- Diagnosis of zoonotic diseases
- Identification of determinant for host specificity
- Molecular basis of pathogenicity
- Development of rapid and highly sensitive detection methods of zoonotic pathogens



Division of Bioresources

- Preservation and supply of zoonotic pathogens, cells, genes, antibodies and animal strains
- Development of prevention and treatment methods for zoonoses



Division of Collaboration and Education

- Coordination of collaboration programs with international and domestic organizations
- Training of experts for the control of zoonoses
- Improvement of IT infrastructure for the international collaboration for research and education



Hokudai Center for Zoonosis Control in Zambia

- Identification of natural host animals and transmission routes of zoonotic pathogens in Africa
- Comprehensive screening of unknown pathogens in Africa
- Prevention and control of zoonoses



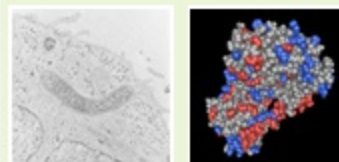
Division of Bioinformatics

- Prediction of outbreaks and epidemics of zoonoses
- Computational analysis of genetic information and protein structure of zoonotic pathogens
- Database development of genetic information of zoonotic pathogens



Division of Infection and Immunity

- Investigation of host response against zoonotic pathogens
- Structural analysis of molecules of pathogens and cellular factors
- Development of novel strategies for therapeutic and prophylactic methods



Unit of Risk Analysis and Management

- Risk assessment of zoonotic events and establishment of useful tools for risk management
- Planning and implementation of proper risk management scheme
- Suggestion of sampling strategy for monitoring zoonotic events



Laboratory for Biologics Development

- Research and education on immunology and infection
- Research and development of vaccines and drugs for infectious diseases



Unit of International Cooperation

- Development of international cooperation
- Management of safety and health in the research and educational environment



FOR THE CONTROL OF ZOONOSES

**Identification of natural host &
elucidation of the route of transmission**

CONTROL OF ZOONOSES

**Development of measures
for diagnosis and
prevention**

**Clarification of the
molecular basis of
pathogenesis**

Collaboration with WHO, FAO and OIE for the Control of Zoonoses



In 2010 Dec, Prof Hiroshi Kida hosted the regional workshop on collaboration between human and animal health sectors on zoonoses prevention and control, in which the members from World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), and World Organisation for Animal Health (OIE) got together for the first time in the world. This was **the 1st Asia Pacific Workshop on Multisectoral Collaboration for the Prevention and Control of Zoonoses.**



WHO Collaborating Centre for Zoonoses Control



In 2011 Nov, WHO designated the Hokkaido University Research Center for Zoonosis Control as the **“WHO Collaborating Centre for Zoonoses Control”**, and Professor Kida is the Head of the Center. The inauguration ceremony and “the regional forum of collaborating/ reference centres on emerging infectious diseases and zoonoses” was held in 2011 Dec. This was **the 2nd Asia Pacific Workshop on Multisectoral Collaboration for the Prevention and Control of Zoonoses.**

How to control avian influenza and how to prepare for future pandemics

1. Why have the H5 HPAIVs persisted in poultry for 19 years and been antigenic variants selected ? Misuse of Vaccine

2. Will the HPAIVs returned to migratory birds persist in nature ?

Contamination of HPAIVs in the nesting lakes of migratory ducks must have occurred. Prompt eradication of the H5N1 HPAIVs from poultry in Asia is urgently needed.

3. How should avian influenza be controlled ?

For the containment and eradication of avian influenza viruses in the poultry flocks infected, enhanced surveillance, early detection, culling the flock, movement restriction, and strengthening hygiene without misuse of vaccine should be done.

Vaccine should be carefully used in addition to, not instead of stamping out.

4. Will H5N1 HPAIV and H7N9 LPAIV cause pandemic influenza?

It is unlikely to occur; direct transmission of AIV from birds only to specific humans who have receptor for avian strains, and thus human-human transmission may not occur, but may occur via pigs. H5N1 or H7N9 are not only candidates of pandemic strains.

5. Are the measures for the control of seasonal flu satisfactory ?

How to control pandemic influenza should be based on the measures for the control of seasonal influenza. Especially seasonal flu vaccines should be drastically improved since current split vaccines prepared by ether- or detergent-disruption are not immunogenic enough.

★ Global surveillance of avian, swine and human influenza, and drastic improvement of seasonal flu vaccines are of crucial importance.

Library of pandemic flu vaccine strain candidates

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16
N1																
N2																
N3																
N4																
N5																
N6																
N7																
N8																
N9																

 Virus isolated from a waterfowl (75 combinations)

 Virus generated in the laboratory (69 combinations)

Influenza viruses of 75 combinations of the HA and NA subtypes have been isolated from fecal samples of ducks in Alaska, Siberia, Mongolia, Taiwan, China and Japan (black).

69 combinations were generated by genetic reassortment in the lab (red).

Test vaccines prepared from H1N1, H5N1, H6N2, H7N7, H7N9 and H9N2 viruses in the library conferred sufficient immune response to protect chickens, mice, and macaques from the challenge with isolates from poultry birds and humans.

Thus we have now vaccine strains for pandemic influenza.

2,900 avian influenza viruses of 144 combinations of HA and NA subtypes have been stocked as vaccine strain candidates. Their pathogenicity, antigenicity, genetic information and yield in chicken embryo have been analyzed, databased, and opened at Web site (<http://virusdb.czc.hokudai.ac.jp/vdbportal/view/index.jsp>).

Jan 26, 2015

National Project for the development of effective and safe **seasonal influenza vaccines**

Industry-University-Government Collaboration

All-Japan Influenza Vaccine Study Group



- Japan Agency for Medical Research and Development
- Ministry of Education, Culture, Sports, Science and Technology
- Ministry of Health, Labor and Welfare



- Comparison of the immunological activity/potency of WPVs with the current SVs
- Preclinical studies
- Clinical studies
- Improvement of Biological standard

Summary of the results of assays on the test vaccines provided by the producers

Immunological activity	Producer A		C		D	
	SV	WPV	SV	WPV	SV	WPV
Induction of cytokines	-	++	-	++	-	++
Activation of dendritic cells	-	+++	-	+++	-	+++
Activation of T cells	-	+	-	+	-	-
Specific antibody response	-	+++	-	+	-	++
Protection against challenge	-	+++	-	+++	-	+++

SV: Ether-split vaccine

WPV: Inactivated whole virus particle vaccine

Summary

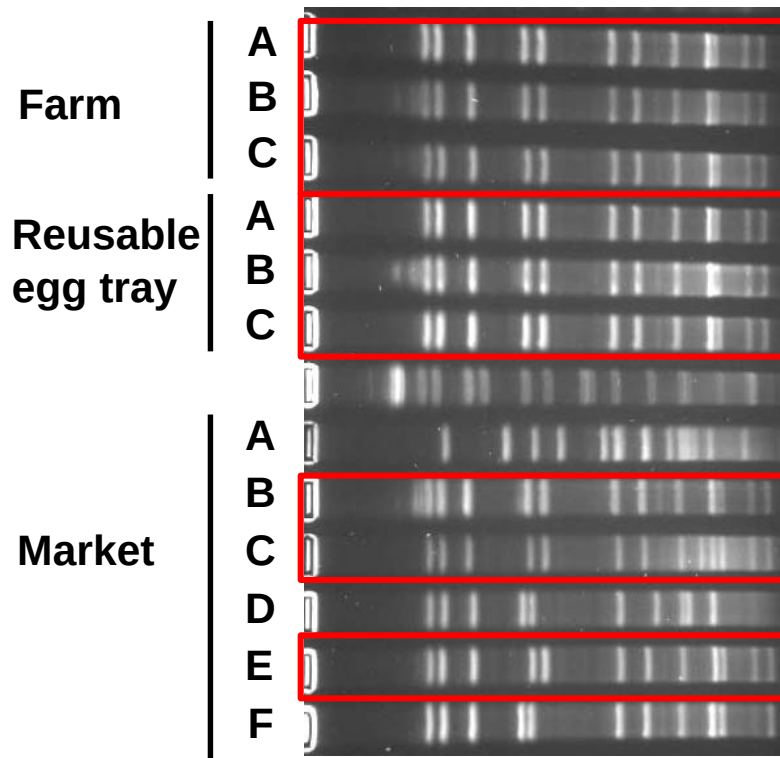
- Inactivated whole virus particle vaccines (WPV) induced much higher adaptive immune responses than split vaccines (SV) in mice and monkeys.
- WPV conferred protective immunity from homologous influenza virus challenge in mice.
- WPV induced much greater cytokine responses 3-6 hours after vaccination than SV in mice.
- WPV enhanced surface expression of CD86 on DCs.

Conclusion

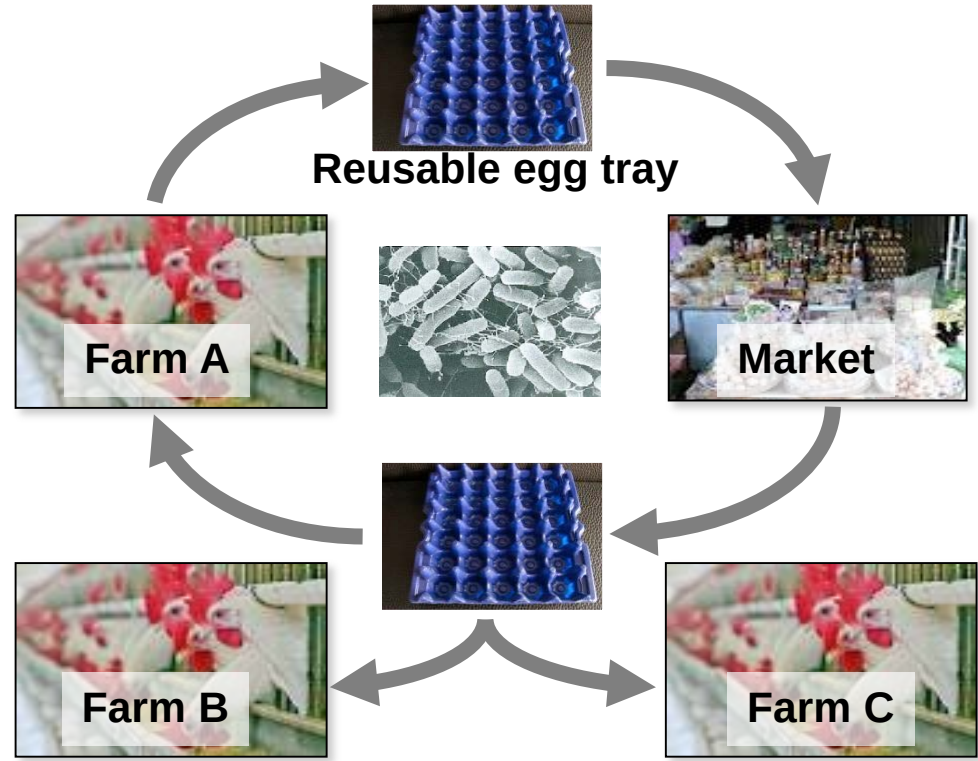
WPV stimulated the innate and adaptive immune systems much more efficiently than SV vaccines in mice and monkeys.

 **Preclinical and clinical studies**

Transmission of **antimicrobial resistant** *Salmonella*



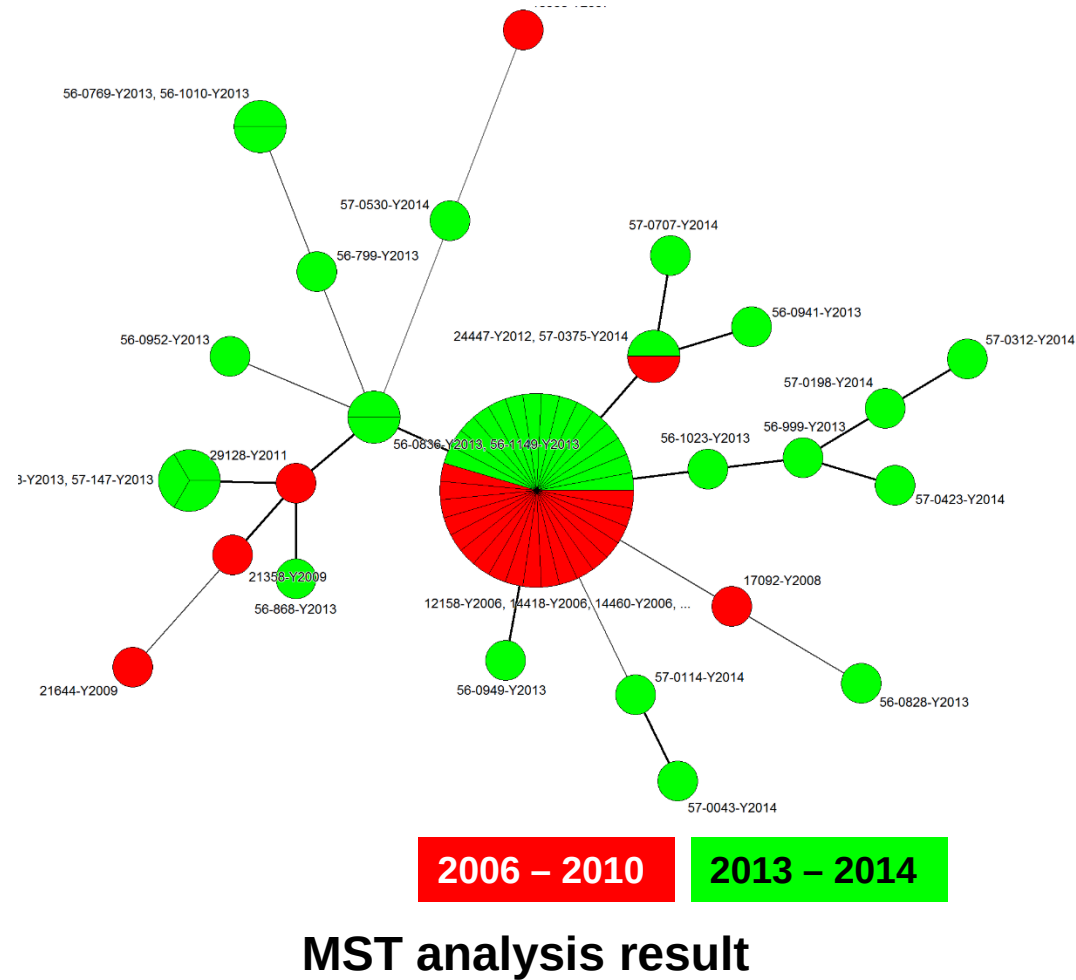
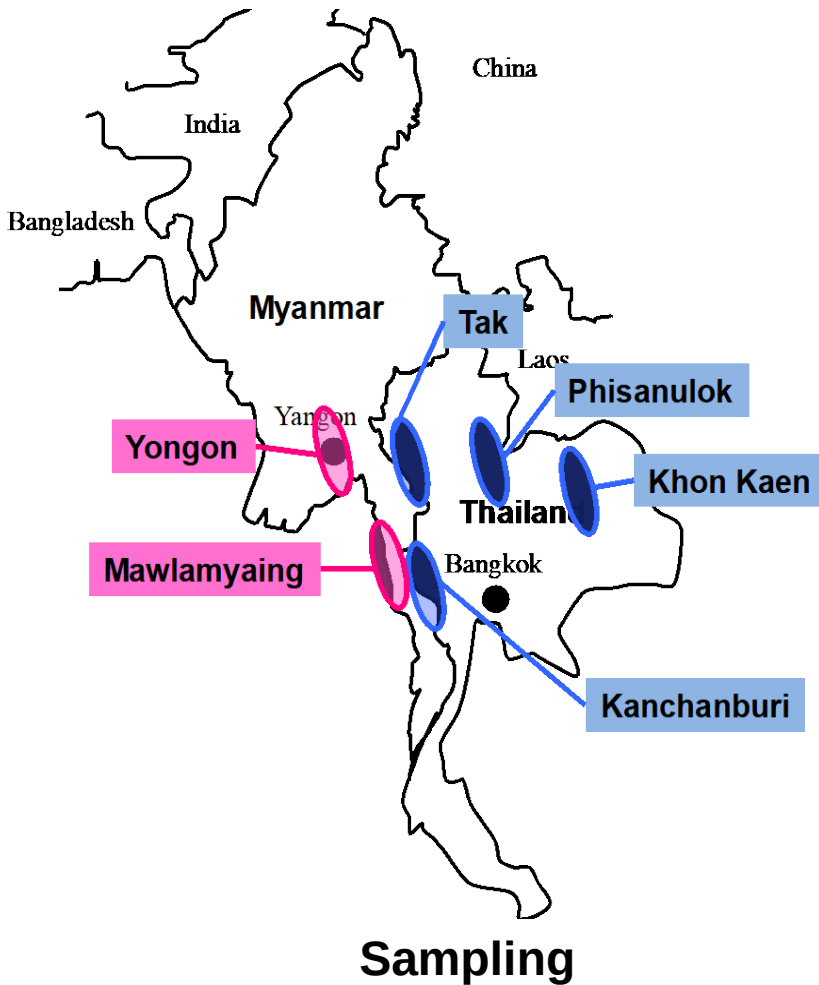
PFGE results of *Salmonella* isolates



Possible spread route

Molecular epidemiological analysis of multidrug-resistant *Salmonella* isolates using Pulse Field Gel Electrophoresis (PFGE) revealed the possible role of **reusable egg tray** on the spread among farms in Thailand.

Multidrug-resistant tuberculosis outbreak at Thai-Myanmar border

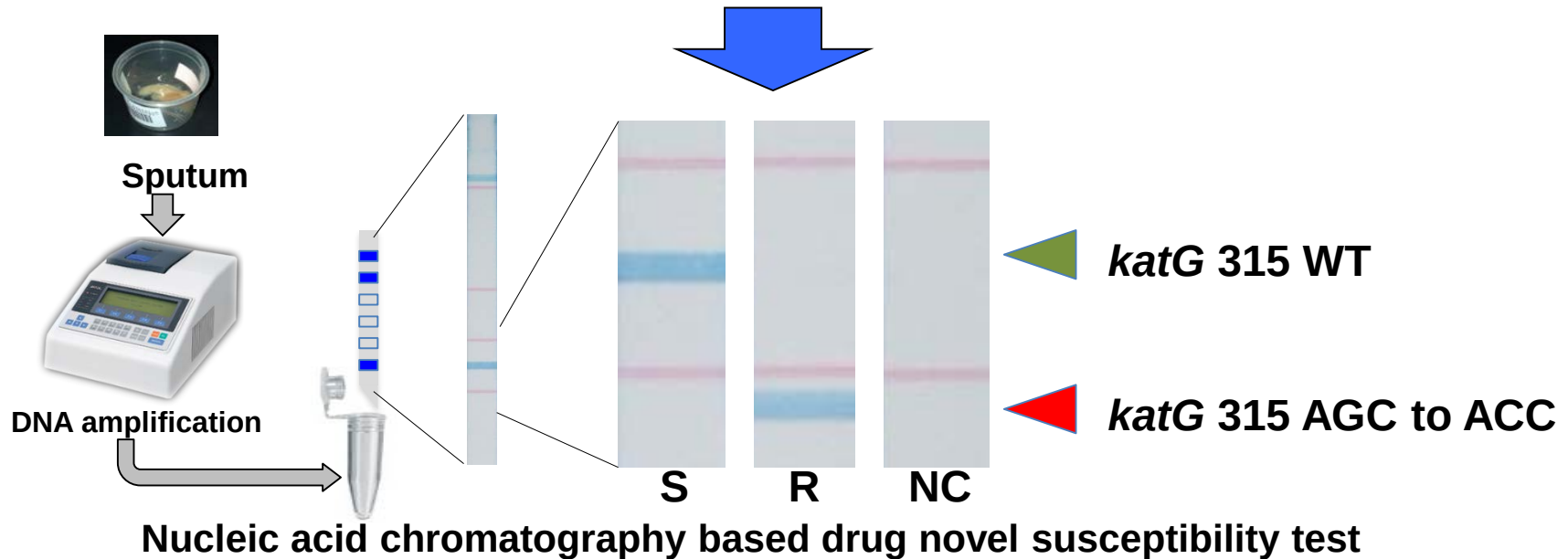


Minimum spanning tree (MST) analysis using Multi Locus Variable Number Tandem Repeat Analysis (MLVA) data revealed the **long term** and **trans-border spread** of a **Beijing type** multidrug-resistant *Mycobacterium tuberculosis* strain at Thai-Myanmar border.

Development of rapid **drug susceptibility test** of *M. tuberculosis*

Mutations associating to **isoniazid resistance** found in clinical isolates from Zambia

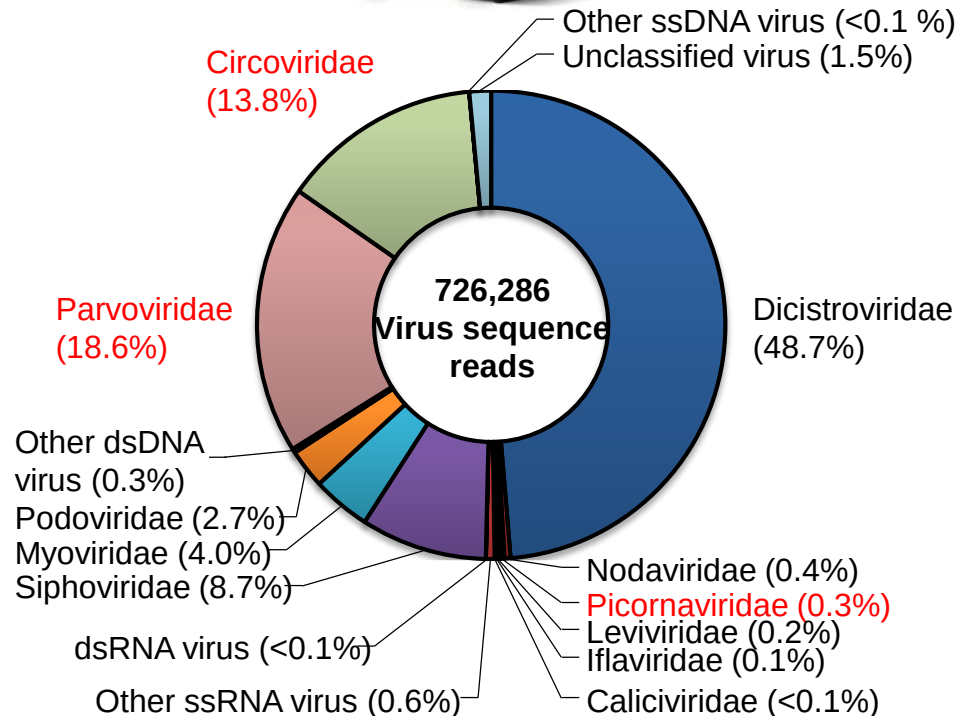
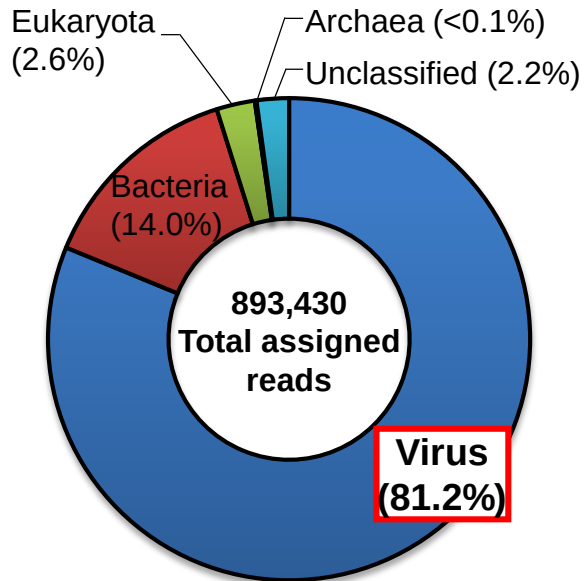
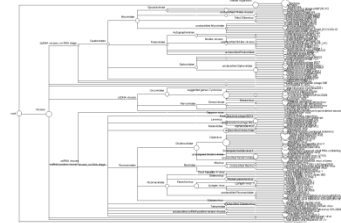
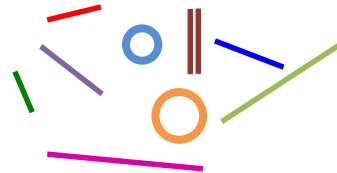
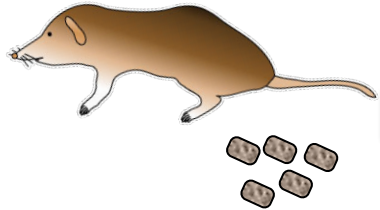
Locus	Amino acid change(s)	Nucleotide change(s)	No. of isolates INH ^r (n=100)	No. of isolates INH ^s (n=48)
<i>katG</i> 315	Ser to Thr	AGC to ACC	89	0
<i>katG</i> 315	Ser to Asp	AGC to AAC	4	0
<i>katG</i> 315, <i>inhA</i> -15	Ser to Thr, N/A	AGC to ACC, C to T	1	0
<i>katG</i> 329, <i>inhA</i> -15	Asp to Glu, N/A	GAC to GAA, C to T	1	0
Wild type	None	None	5	48



We developed a **rapid, simple and low cost** drug susceptibility test for *Mycobacterium tuberculosis* based on the data obtained by the analysis of clinical isolates from 11 countries. This method can be a **Point-of-Care test** for choosing treatment regimen.

Metagenomic analysis of shrew feces

- Sampling of shrew feces
- Filtration of fecal suspension
- Nuclease treatment
- Virus DNA / RNA extraction
- High-throughput sequencing
- Bioinformatics analysis

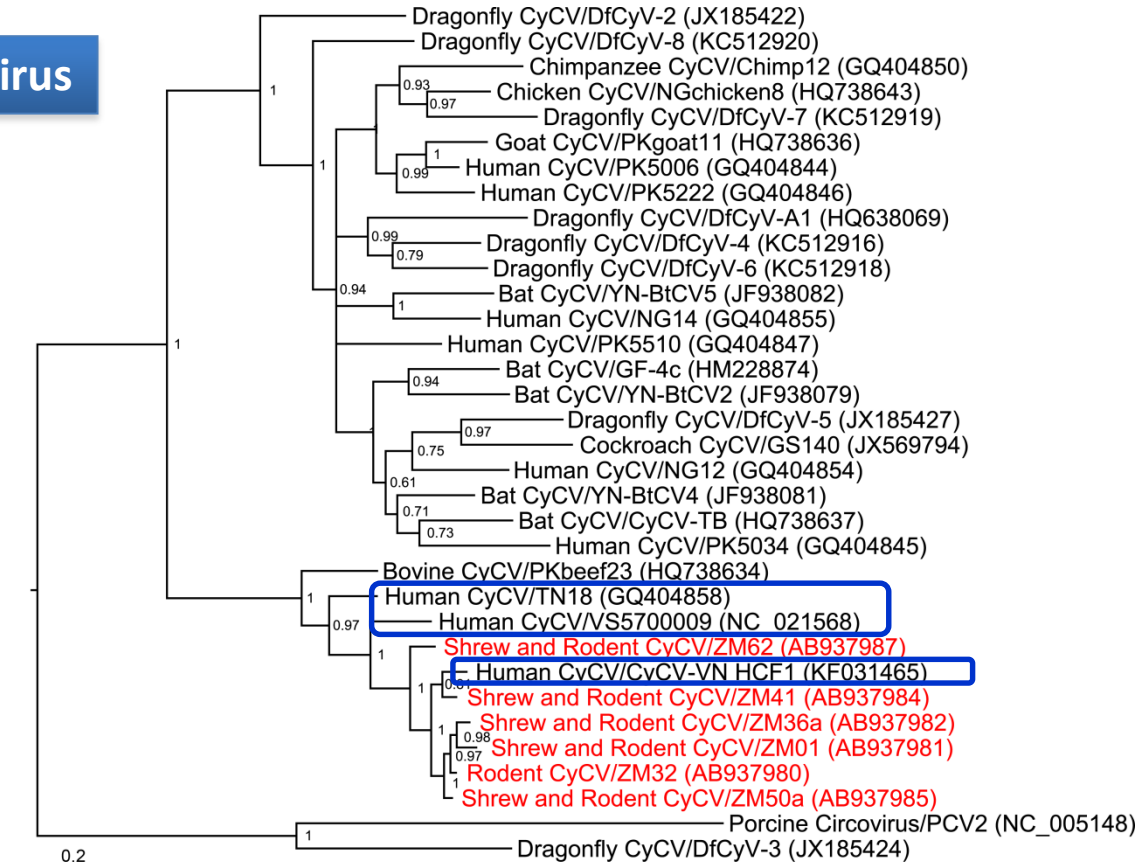
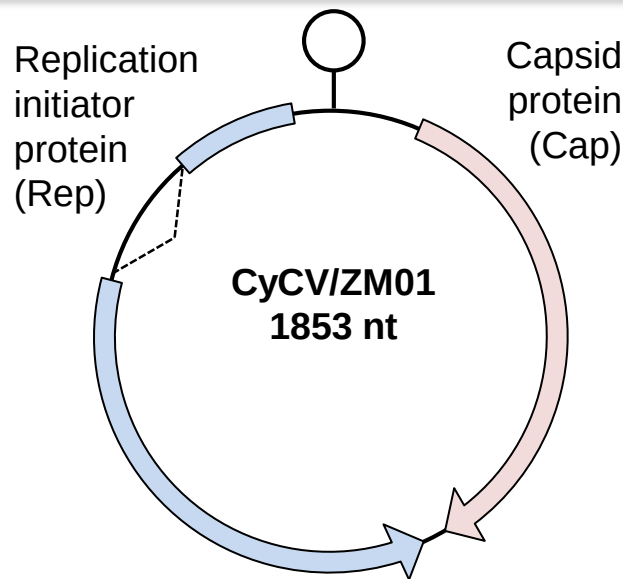


- Viral nucleic acids were enriched by the filtration and nuclease treatment.
- Novel mammalian viruses were identified from the sequence reads assigned as *Circoviridae*, *Parvoviridae*, and *Picornaviridae*.

Identification of **novel cycloviruses** from shrew

Phylogenetic analysis of the full-length amino acid sequence of Rep protein of cyclovirus

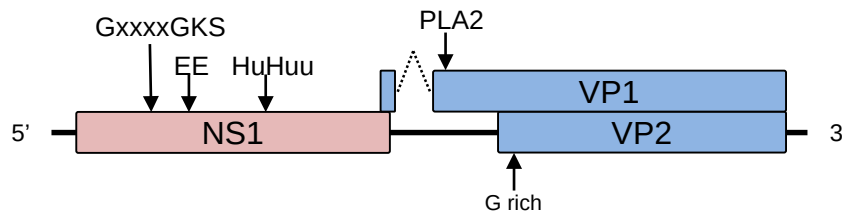
Genome organization of shrew cyclovirus



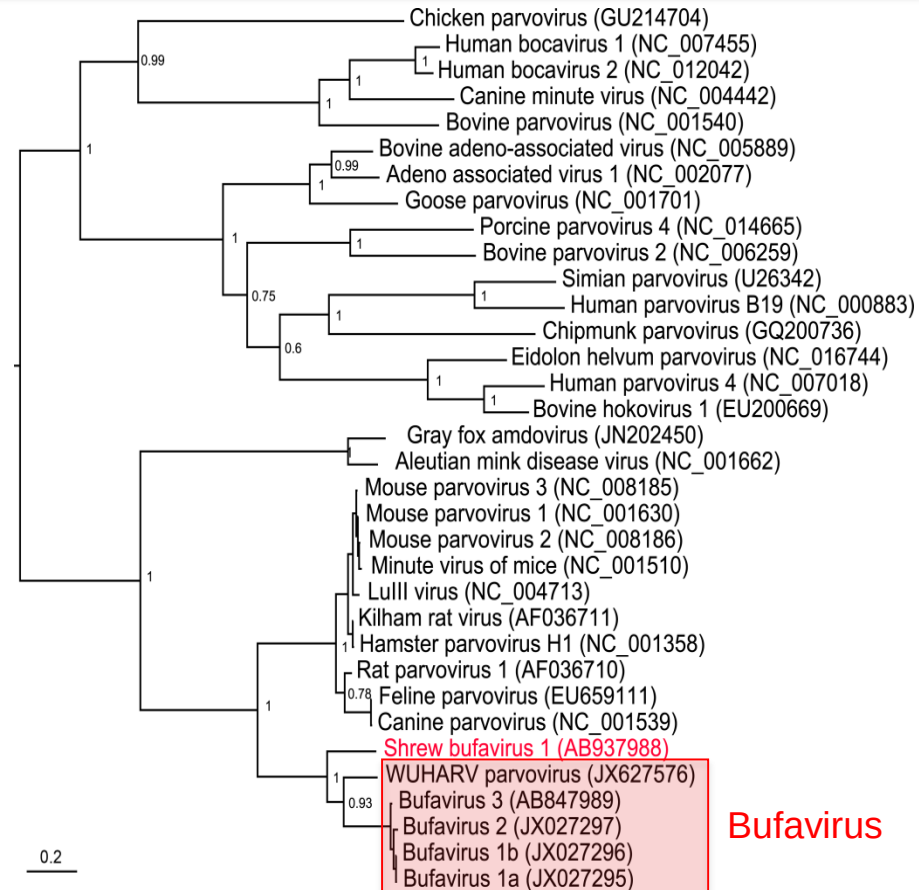
- We identified several novel cycloviruses, which are variants of human cycloviruses detected in cerebrospinal fluid from patients with suspected central nervous system infections or unexplained paraplegia.

Identification of **novel parvovirus** from shrew (**Shrew bufavirus 1**)

Genome organization of Shrew bufavirus 1



Phylogenetic tree based on the VP2 of parvovirus



- Bufavirus, a recently described parvovirus, was initially discovered in the feces of a child with diarrhea in Burkina Faso in 2012, and adults with gastroenteritis in Bhutan, Finland and Netherland in 2014.
- We identified novel parvovirus from shrew (Shrew bufavirus 1) which is related to human bufavirus.
- This is the first report of human bufavirus-related parvovirus in wildlife.

Identification of novel viruses in wild animals in Zambia

	species	family	genus	Isolated/d etected	pathogenesis	Wild animals	Tissues
Hemorrhagic fever-related virus	Leopards Hill virus (LPHV)	Bunyaviridae	Nairovirus	isolated	virulent to mice	Insectivore bats (<i>Hipposideros gigas</i>)	Liver, Lung
	Luna virus	Arenaviridae	Arenavirus	isolated	avirulent to mice	Mastomys (<i>Mastomys natalensis</i>)	Kidney
	Lunk virus	Arenaviridae	Arenavirus	isolated	avirulent to mice	African pigmy mouse (<i>Mus minutoides</i>)	Kidney
	Solwezi virus	Arenaviridae	Arenavirus	isolated	avirulent to mice	Grammomys rodent (<i>Grammomys sp.</i>)	Kidney
Other viruses	Shrew paramyxovirus	Paramyxoviridae	unclassified	detected	unidentified	Shrew (<i>Crocidura spp.</i>)	Kidney
	Rodent paramyxovirus	Paramyxoviridae	unclassified	detected	unidentified	Mastomys (<i>Mastomys natalensis</i>) and other mouse species	Kidney
	Bat paramyxovirus	Paramyxoviridae	unclassified	detected	unidentified	Fruits bats (<i>Eidolon helvum</i>)	Spleen
	Rodent cyclovirus	Circoviridae	Cyclovirus	detected	unidentified	Mastomys (<i>Mastomys natalensis</i>)	feces
	Shrew cyclovirus	Circoviridae	Cyclovirus	detected	unidentified	Shrew (<i>Crocidura hirta</i>)	feces
	Crohivirus	Picornaviridae	Crohivirus (novel genus)	detected	unidentified	Shrew (<i>Crocidura hirta</i>)	feces
	Bat Adenovirus	Adenoviriade	unidentified	isolated	unidentified	Fruits bats (<i>Rousettus aegyptiacus</i>)	Liver
	Mastmys polyomavirus	Polyomaviridae	Orthopolyomav irus	detected	unidentified	Mastomys (<i>Mastomys natalensis</i>)	Spleen
	Vervet monkey polyomavirus	Polyomaviridae	Orthopolyomav irus	detected	unidentified	Vervet monkey	Spleen, Liver
	Yellow baboon polyomavirus	Polyomaviridae	Orthopolyomav irus	detected	unidentified	Yellow baboon	Spleen, Liver
	Calhevirus 2a	unclassified	unclassified	detected	unidentified	Shrew (<i>Crocidura hirta</i>)	feces
	Calhevirus 2b	unclassified	unclassified	detected	unidentified	Shrew (<i>Crocidura hirta</i>)	feces
	Mfuwe bufavirus	Parvovirus	Protoparvovirus	detected	unidentified	Yellow baboon	Spleen
	Livingstone bufavirus	Parvovirus	Protoparvovirus	detected	unidentified	Chacma baboon	Spleen
	Mpulungu bufavirus	Parvovirus	Protoparvovirus	detected	unidentified	Shrew (<i>Crocidura hirta</i>)	Spleen
	Solwezi bufavirus	Parvovirus	Protoparvovirus	detected	unidentified	Shrew (<i>Crocidura hirta</i>)	Spleen

Points for the control of zoonoses

We must accept the fact that zoonoses are not eradicable infections since the causative pathogens are introduced from wildlife in nature. Such zoonotic infections, therefore, can be controlled only by taking preemptive measures to predict and prevent the outbreaks.

For the establishment of preemptive measures against zoonoses, a prerequisite is to identify natural host animals carrying potential pathogens, and to elucidate the transmission routes and factors involved in the spread and pathogenesis of infections. In addition to promoting basic research on zoonotic diseases, there is a pressing need to develop effective measures for diagnosis, prophylaxis and therapy, to widely disseminate information and technology, and to train experts for the control of zoonoses.

Hokkaido University Research Center for Zoonosis Control, thus, carries out coherent scientific and educational activities for the control of zoonoses under the umbrella of One World, One Health concept.