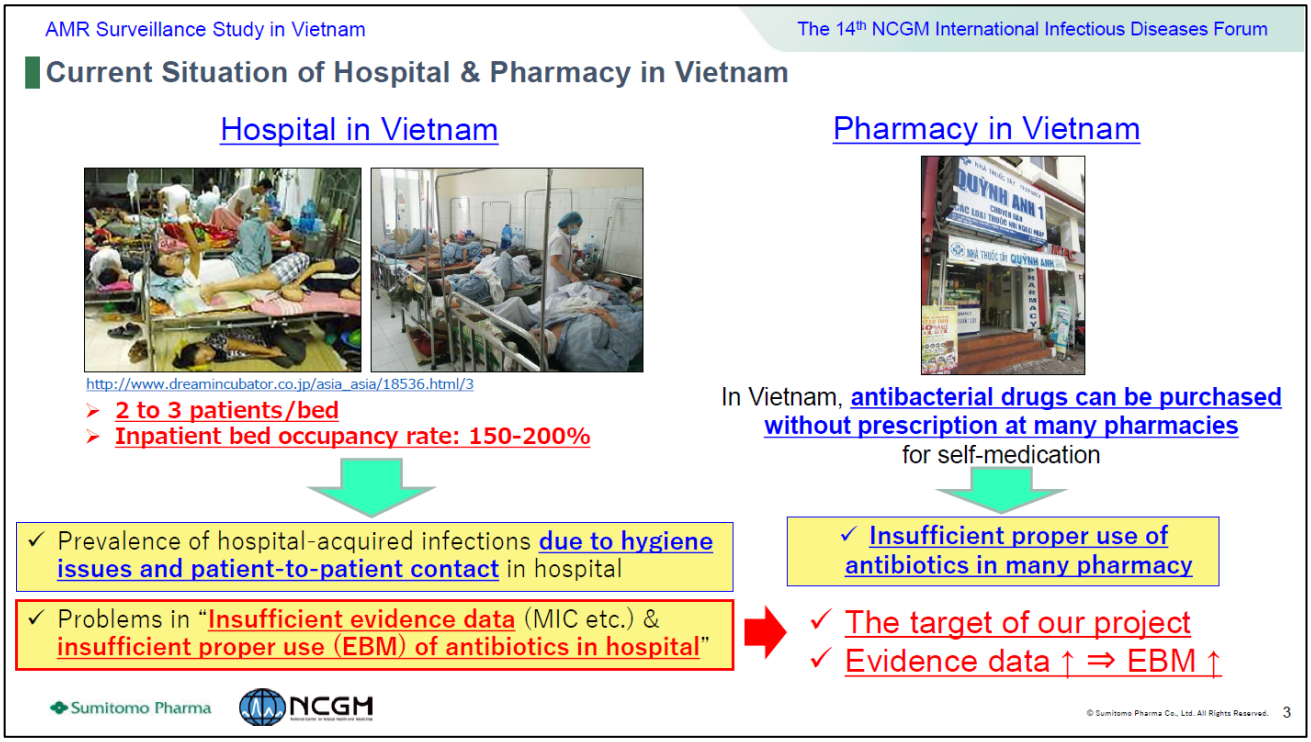
Dr. Kokudo and Dr. Muchanga, thank you very much for such a kind introduction. Can you hear me? Okay. Well, Sumitomo Pharma, about three and a half years ago, we have started the research for AMR in Vietnam. NCGM doctors and our company collaborated for the countermeasures for AMR in Vietnam. So, the current situation is how it has progressed and because of the time constraints, I cannot cover all, but what kind of results are currently available will be covered within my presentation here today.

So, let's move on to the next slide. Okay. First of all, let me cover the background, that is AMR Infection's current status in Vietnam.



I would like you to look at these pictures. This is a general hospital, major hospital we could say, and this is the general ward and ICU status. And, as you see around the beds, the family members are staying. As you see on one bed, there are a couple of patients resting. So, as you see clearly, it's quite crowded or busy. This means that there is a high level of contact among the patients and also, compared to developed countries, the number of doctors, nurses and such healthcare professionals is quite limited. So, even if you go to big hospitals, it's very difficult to get thorough treatment. Therefore, EBM-based antibacterial usage is difficult to conduct.

Also, though this is common to Western Asian countries, antibacterial drugs are available in the market in many pharmacies and community, and there is no prescription necessary. So, there were no observations done by professionals for antibacterial drug usage. That's why this kind of AMR situation happens. In this situation, Sumitomo Pharma and NCGM work collaboratively for the promotion of EBM about the usage of the drugs in the hospital, so that we can contribute to the reduction of AMR situation.

Clinical Problem of Carbapenem-resistance in Vietnam（COMPACT II study）

Comparative in vitro activity of carbapenems against major Gram-negative pathogens: results of Asia-Pacific surveillance from the COMPACT II study
（*International Journal of Antimicrobial Agents*, Volume 39, Issue 4, April 2012, Pages 311-316）

Clinical strains isolated from 3 hospital in Vietnam in **2010**.
- ◆ *Pseudomonas aeruginosa* : 90 strains
- ◆ Enterobacteriaceae : 71 strains
- ◆ *Acinetobacter baumannii* : 19 strains

Prevalence (%) of carbapenem non-susceptible Gram-negative pathogens.

Country	*Pseudomonas aeruginosa*	Enterobacteriaceae	*Acinetobacter baumannii*	All isolates
New Zealand	10.3	12.5	–	11.7
Philippines	31.1	2.9	25.0	18.9
Singapore	23.3	4.2	90.5	22.1
Thailand	28.7	0.4	76.3	22.2
Vietnam	46.7	5.6	89.5	35.0
Overall	29.8	2.8	73.0	23.0

◆ The carbapenem-resistant rate of *P. aeruginosa* isolated in Vietnam was remarkably higher (46.7%) than those in other 4 countries (10.3% - 31.1%) .

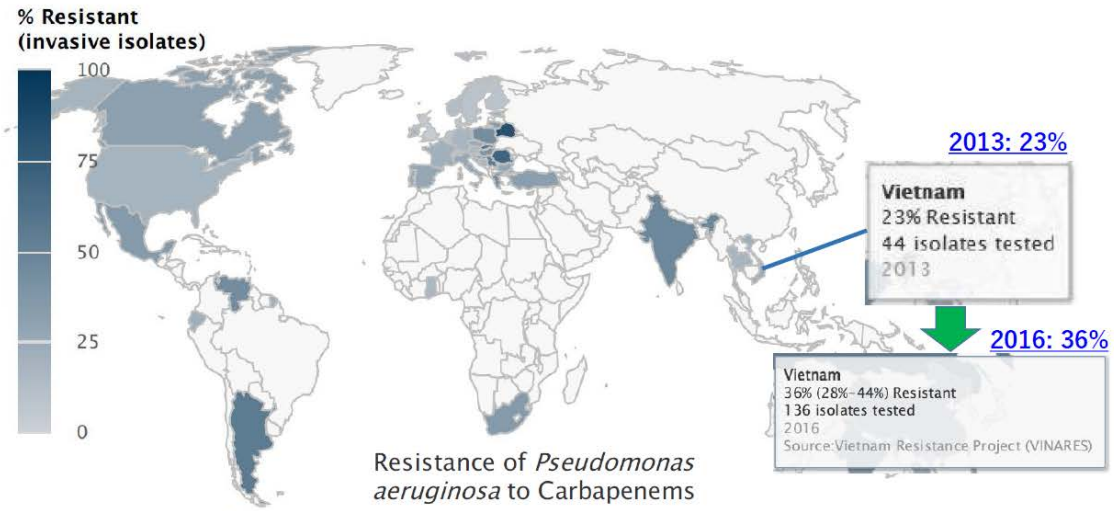
Sumitomo Pharma NCGM

Ten years before, we started our activities and this kind of study data became available. This is the data in 2010. Sorry, this is quite a busy slide. Southeastern Asian countries are seen here and the result look like this. So, in the case of Pseudomonas aeruginosa, carbapenem-resistance accounts for 47%; that is extremely high compared to other countries. For Acinetobacter, well, overall, you see the susceptibility is very high, but in the case of Vietnam, it is as high as 89.5. However, this data is obsolete. So, there was really an issue about what was actually happening at the time when we wanted to start our activities.

ResistanceMap

Resistance of *Pseudomonas aeruginosa* to Carbapenems

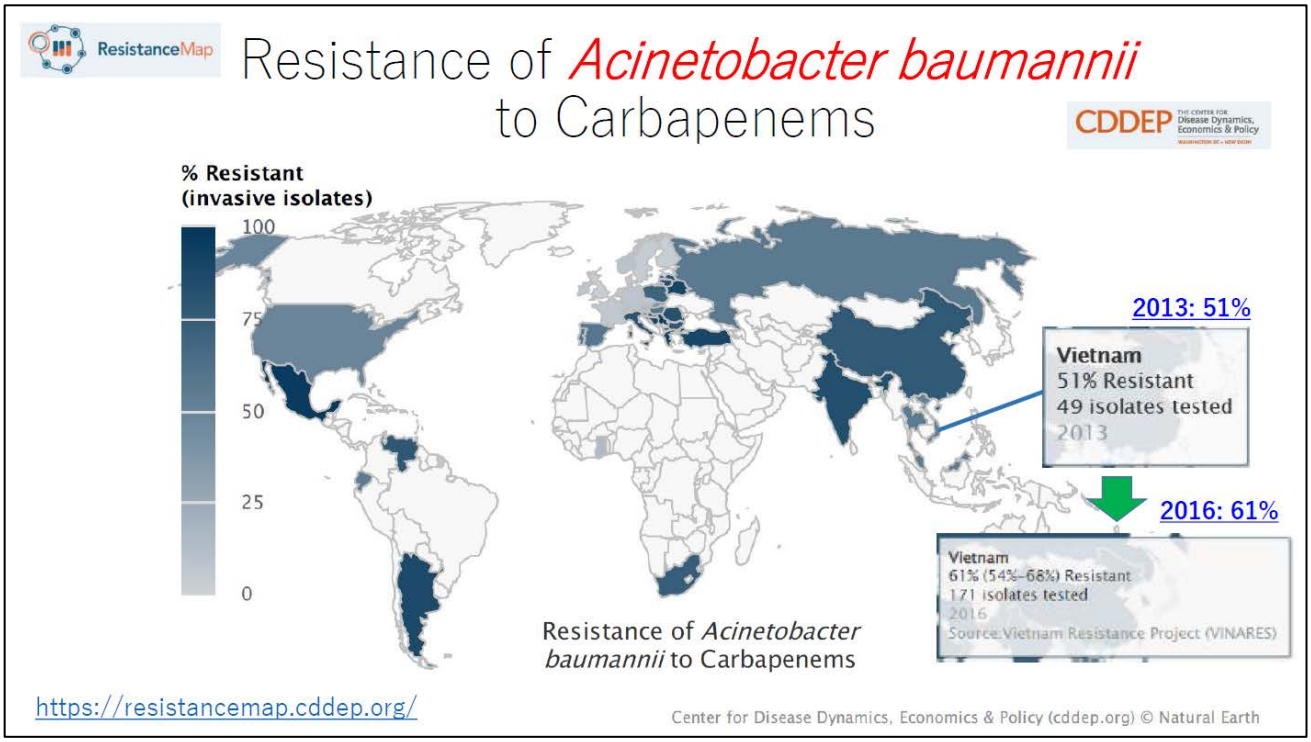
CDDEP Center for Disease Dynamics, Economics & Policy



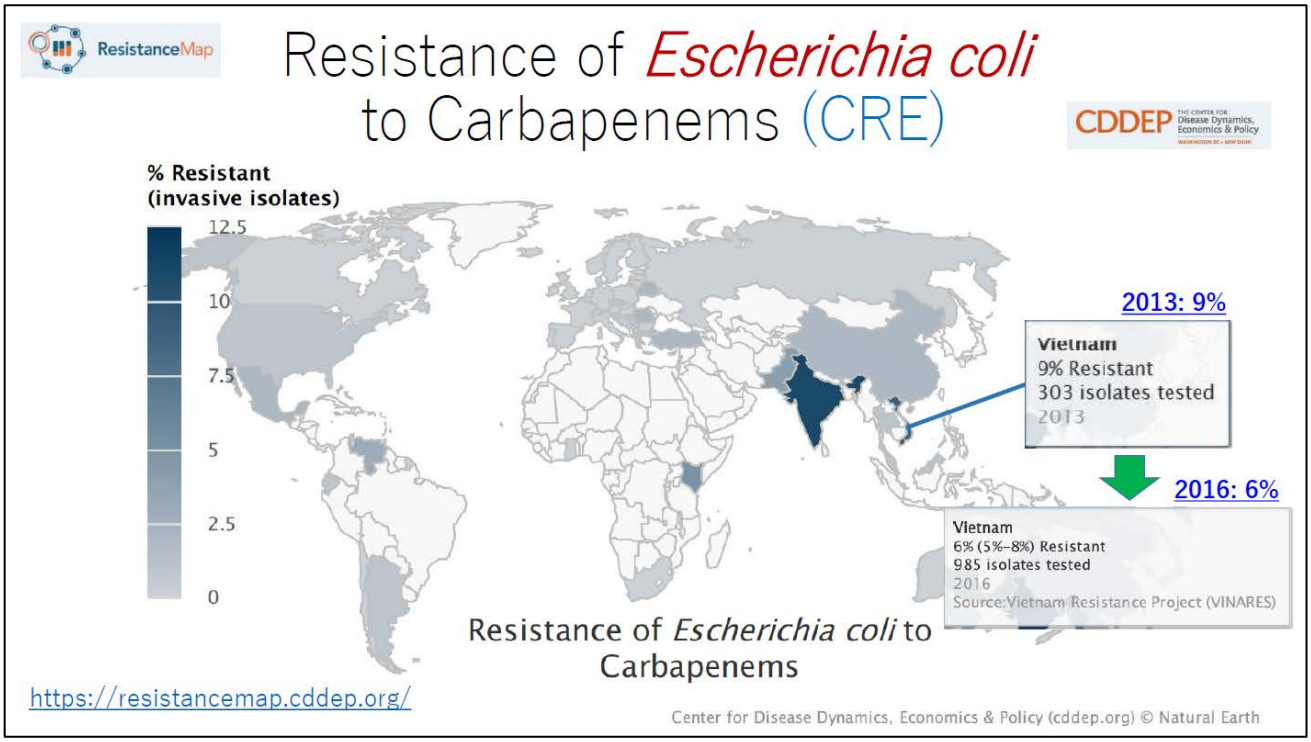
https://resistancemap.cddep.org/

Center for Disease Dynamics, Economics & Policy (cddep.org) © Natural Earth

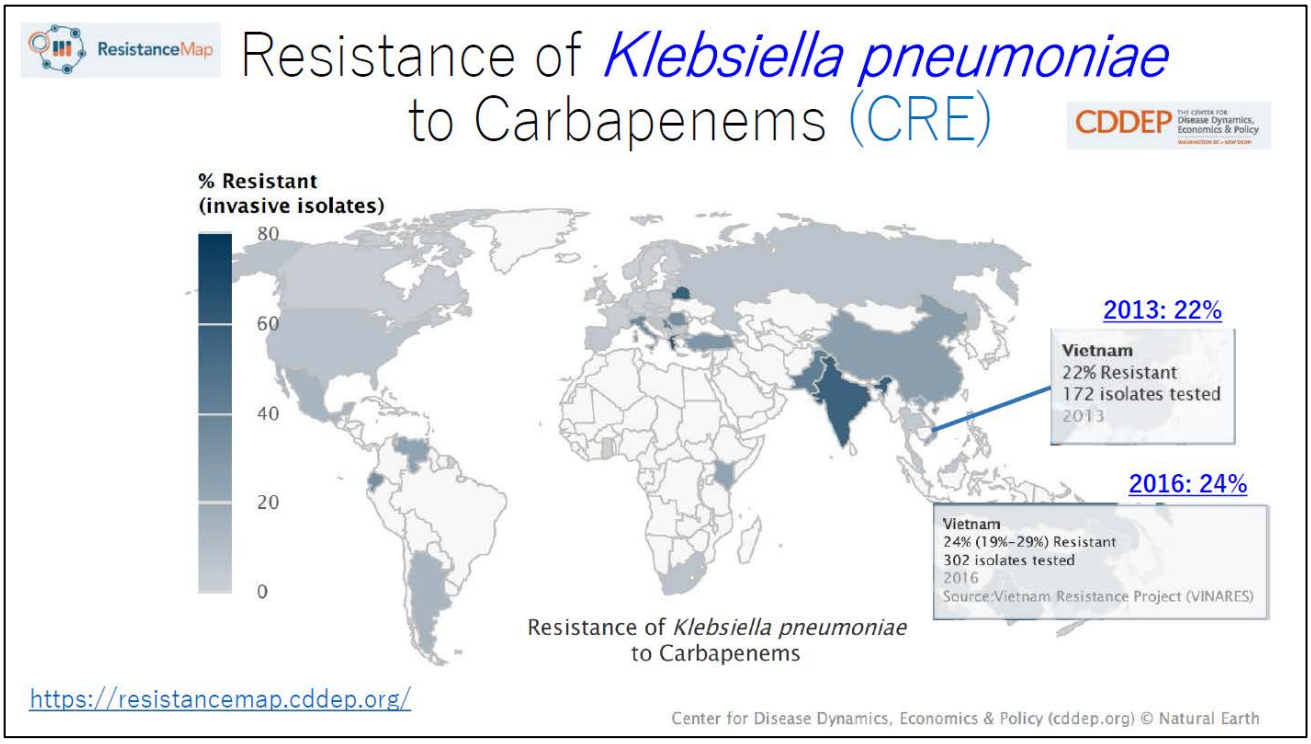
Well, CDDEP came up with this result, probably you may know about this. This is a resistance map. This is a 2013 data. Carbapenem-resistant Pseudomonas aeruginosa accounts for 23% and that increased to 36% in 2016.



This is Acinetobacter baumannii: 2013 – 51% and up to 61% in 2016.

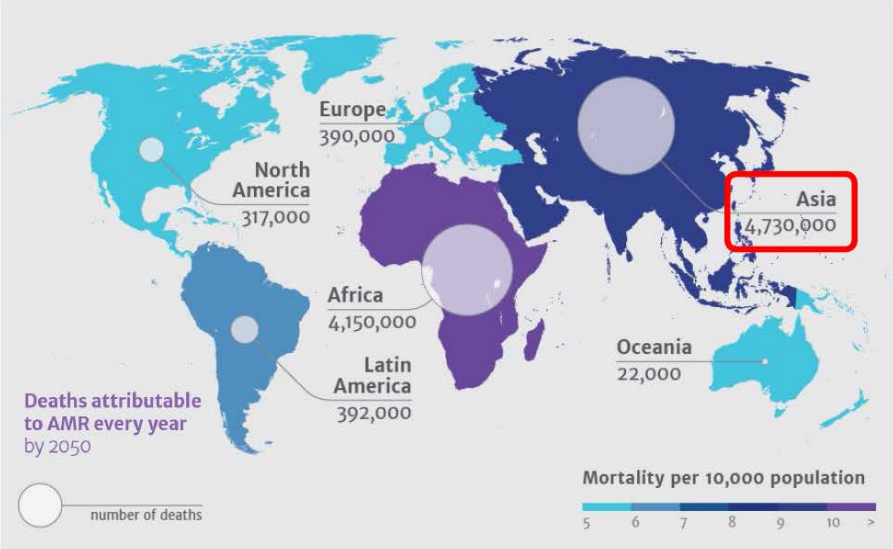


This is carbapenem-resistant E. coli, as shown here. Relatively the resistant rate is lower, in 2013 it's 9% and 2016 – 6%. This could be one of the characteristics of the situation of drug resistance.



Within the same antibacterial, when it comes to Klebsiella pneumoniae, 2013 – 22% and that went up to 24% in 2016. Stably, the number remained high.

Deaths Attributable to AMR Every Year by 2050



Asia
4.73 million
per year

I am sure that you have seen this report quite frequently. It is often quoted. If these are left as they are; in 2050, Asia will have 4.73 million deaths per year due to AMR infection. Compared to other areas in the world, you see, Asia seems to have quite a grave situation and Vietnam contributes to this number as well.

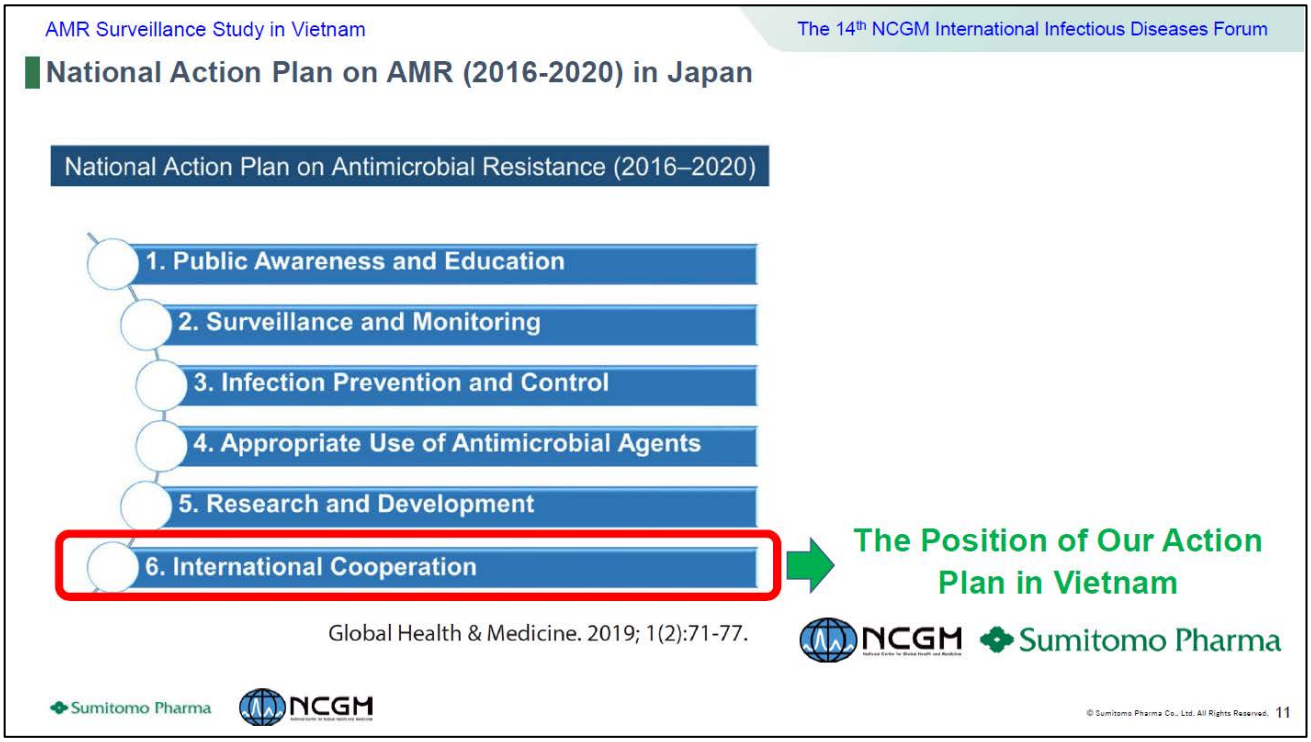
The 1st National Action Plans on AMR in each country

FIGURE 2 | National action plans on antimicrobial resistance (AMR) across the globe

Source: *Antimicrobial Resistance. Library of National Action Plans.* World Health Organization (WHO), 2017

Considering this situation, the countries in the world and also Vietnam, including Japan as well, started AMR action plans. Well, Vietnam actually disclosed action plan in 2013; that is

three years earlier than the case of Japan. However, as has been mentioned, there are many factors that speak out for a change or improvement. There is an overcrowding of the patients, so the government of Vietnam is also struggling to solve the situation.

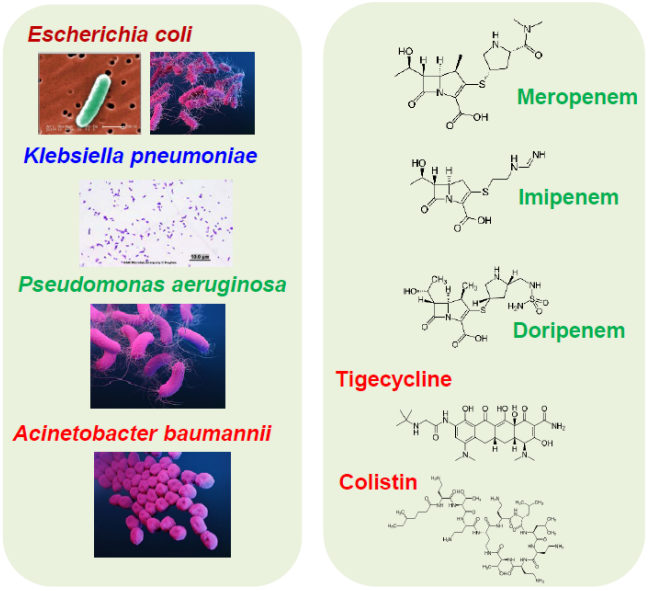


So, considering this situation, we will look at Japan's National action plan. Number six is international cooperation; this is where we want to focus. So, together with NCGM, Sumitomo Pharma became involved in contributing to the improvement of the situation or to proceed with the action plan of Vietnam.

Study Design & Organization of Study Group

With that background, what kind of study design and organization of study groups should be established?

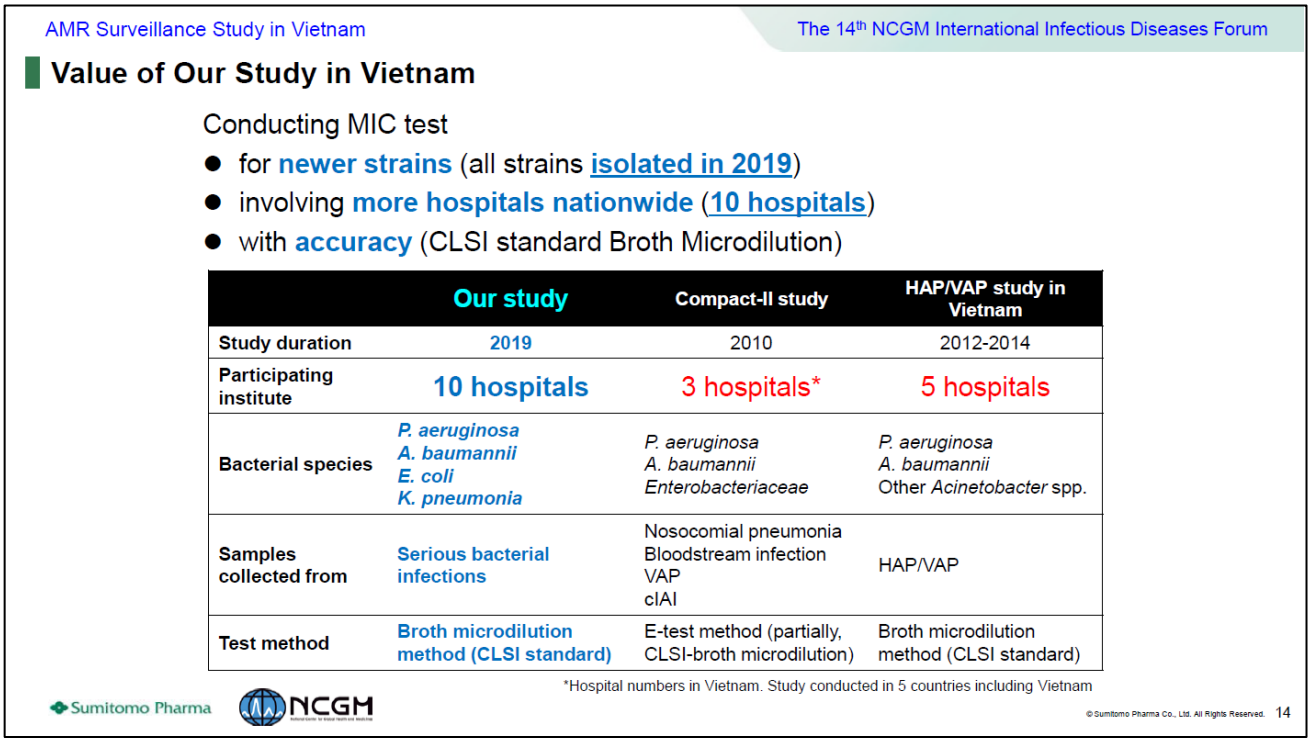
Study design (Summary)



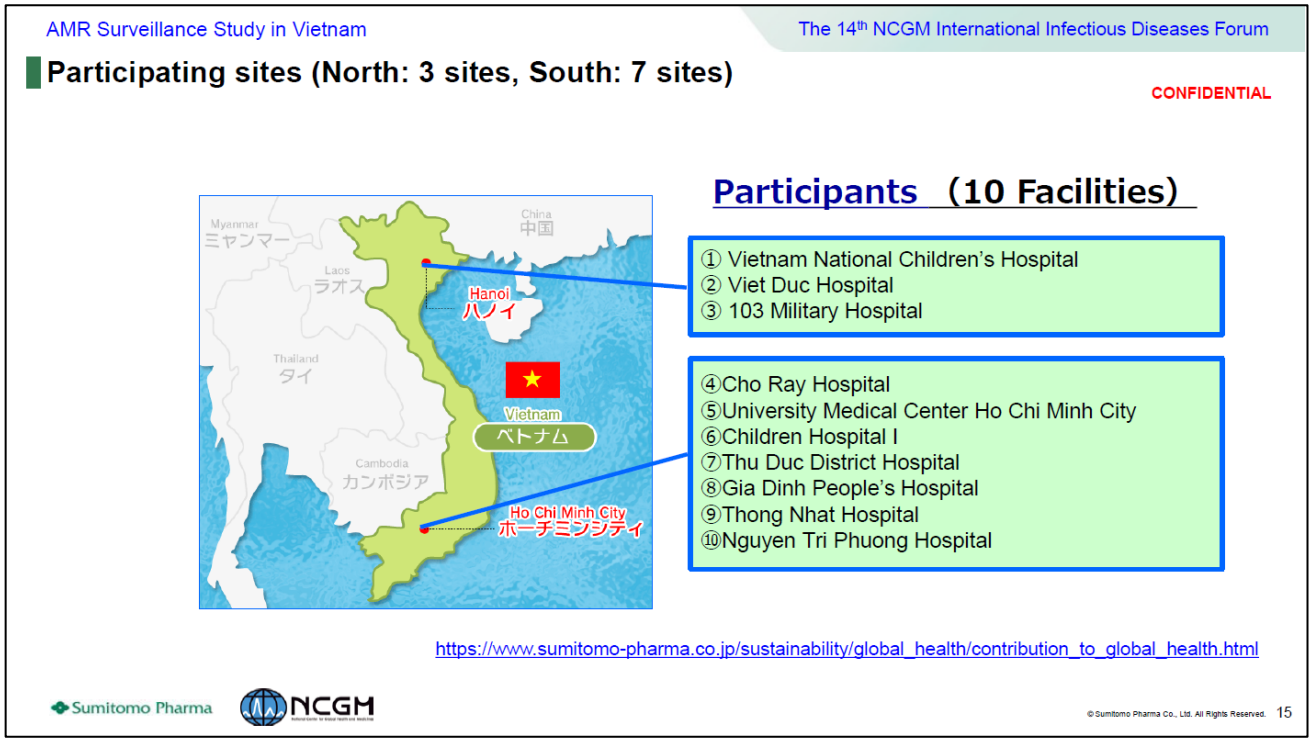
Let me introduce the study design. So, the targeted bacteria are those that are common in the world and the most serious strain that needs to be solved. The Gram-negative bacteria are of four kinds – E. coli, Klebsiella, Pseudomonas aeruginosa, as well as an Acinetobacter baumannii

in South Asia, including Vietnam. Meropenem, Imipenen, Doripenem are used as the major medicine. So, these three are the target drugs. Now for our research, I will talk about a lot of AMR situations. So, in such a situation, tigecycline and colistin are used as a combination with Carbapenem. So these, in total, are the five targets of our research and ordinary MIC collection. And, EU or North American standards are used for the calculation of the resistance. So, that is what we have done for the data analysis.

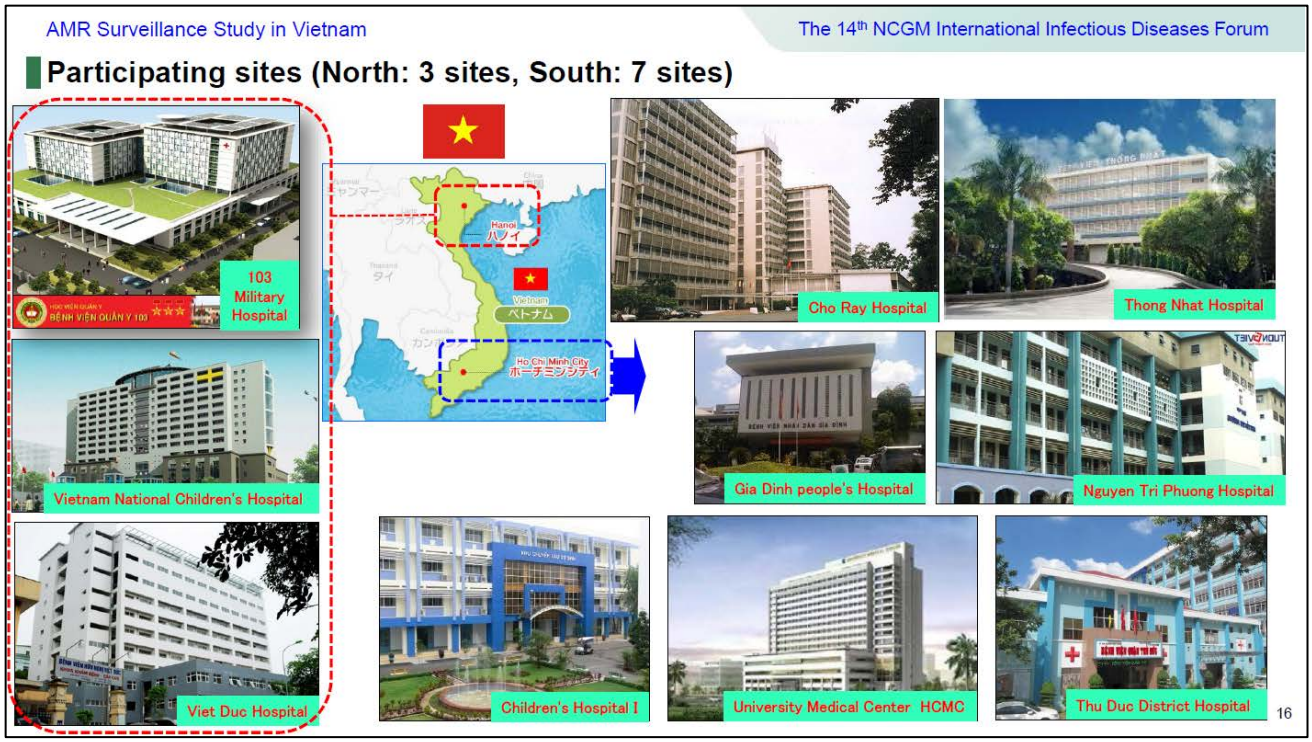
We got the collaboration of the doctors from each site, so that they can understand their situation of the infection. Also in this country, electronic data is quite limited. So, nationwide data analysis is added, and also a north to south regional analysis and site analysis are also introduced in this study. Although this is quite basic,but we wanted to start from the basics. So, that's how we started.



The value of the study shown here, compared to the other studies, is the selection of the sites. Actually, in the previous studies, the participating sites were less. Of course, we wanted to increase the participating sites, but since it is a global study, it is rather difficult. So, we asked 10 sites to participate and also for all samplings. The severely diagnosed patients were studied and samples were collected. And also, similar approaches are shown, but mainly relied on hematology. So, we have looked at other testing methods to use for this project.

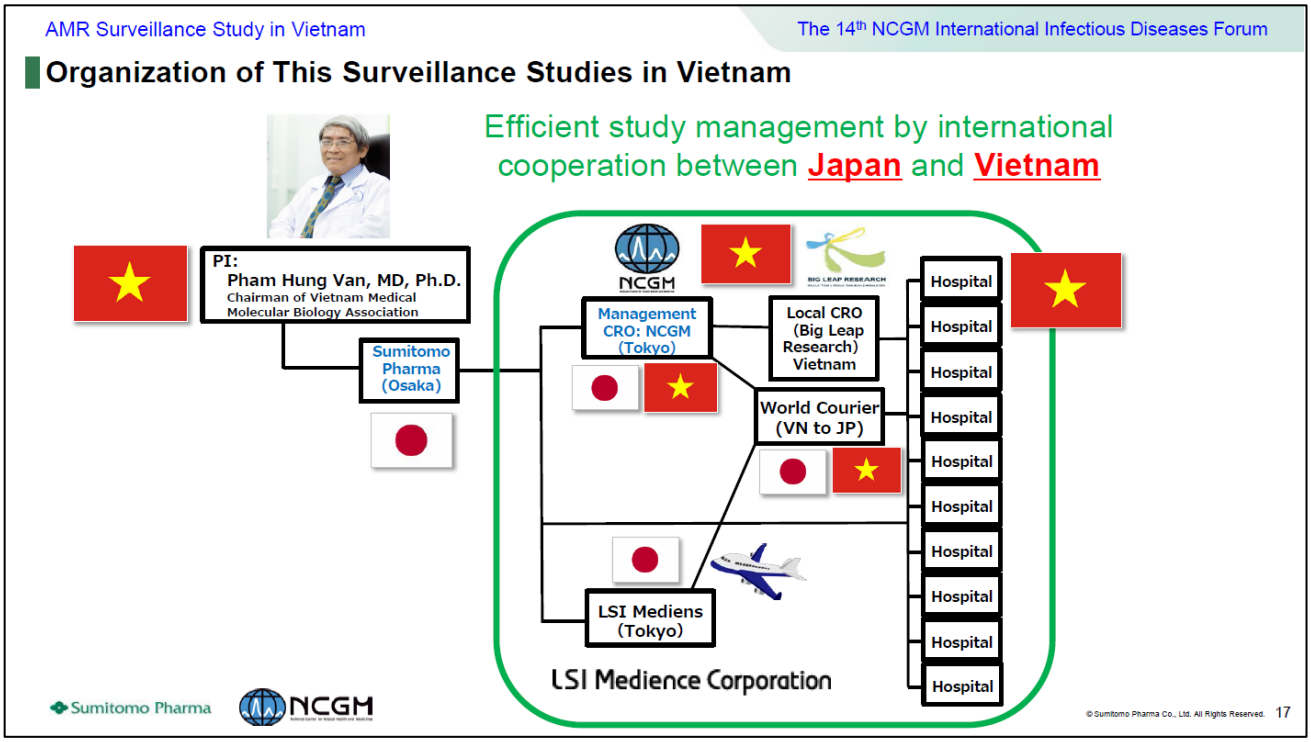


These are the participating sites. In the North, in Hanoi, three sites participated. And for the southern area, in the Ho Chi Minh City, seven sites participated. So, we had seven more sites, with the cooperation of those 10 sites, we have conducted this study.

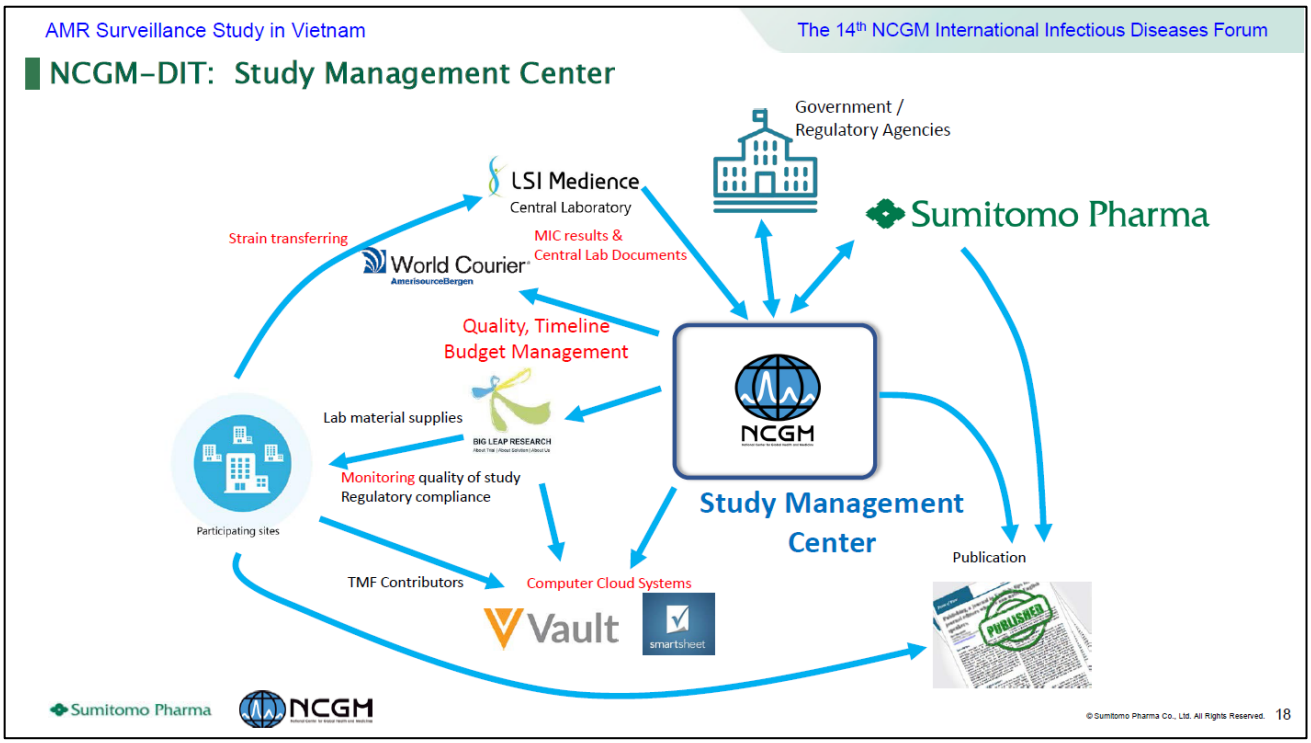


And these are the photos of the hospitals that participated in the study. Vietnam – I don't know what kind of images do you have of this country? Those sites have very modern and state-of-the-art facilities and larger than the Japan sites. And actually, the occupancy rate of the hospital is 150% to 250%. This is the actual situation in the country.

As we proceed with this joint research, not only us but also NCGM doctors will now have many experiences in doing this type of collaborative research,



so, they visited the sites to coordinate the program. Dr. Van, the KOL in Vietnam is designated as the PI. Sumitomo Pharma also coordinates and the overall management is done by NCGM. And in the local areas in Vietnam, local CROs also participated in coordinating with participating sites. Also in the initial phase, all of the strains collected were sent to Tokyo by the World Courier. So, since it's very difficult to do analysis for all of the strains,



we put up this type of infrastructure or scheme of the study. The major role played by NCGM International Trial Group, NCGM DIT acted as the Study Management Center. It also involved Sumitomo Pharma, and the other stakeholders. And for two years, this NCGM Study Management Center coordinated and operated the study.

So, this Study Management Center or this NCGM-DIT played a pivotal role in pursuing this research project.

So, with this framework, we conducted the study. At the initial phase, we had a get together in Hanoi, and President CEO, Nomura participated. This is our PI, Dr. Van, and also Dr. Chan and Dr. Ushio, JICA staff, and also representatives from the Embassy of Japan were also present. In the past, international NGO also participated. So, global stakeholders are quite active in Vietnam. Those entities participated in the operation of the city and various support was provided. On the homepage with this address, the details are shown. So, please visit this website in your leisure time.

Results of the 1st Study (Summary) & Future Plan

Let me show you the results of the first study.

MIC data analysis

(31st ECCMID, 2021)

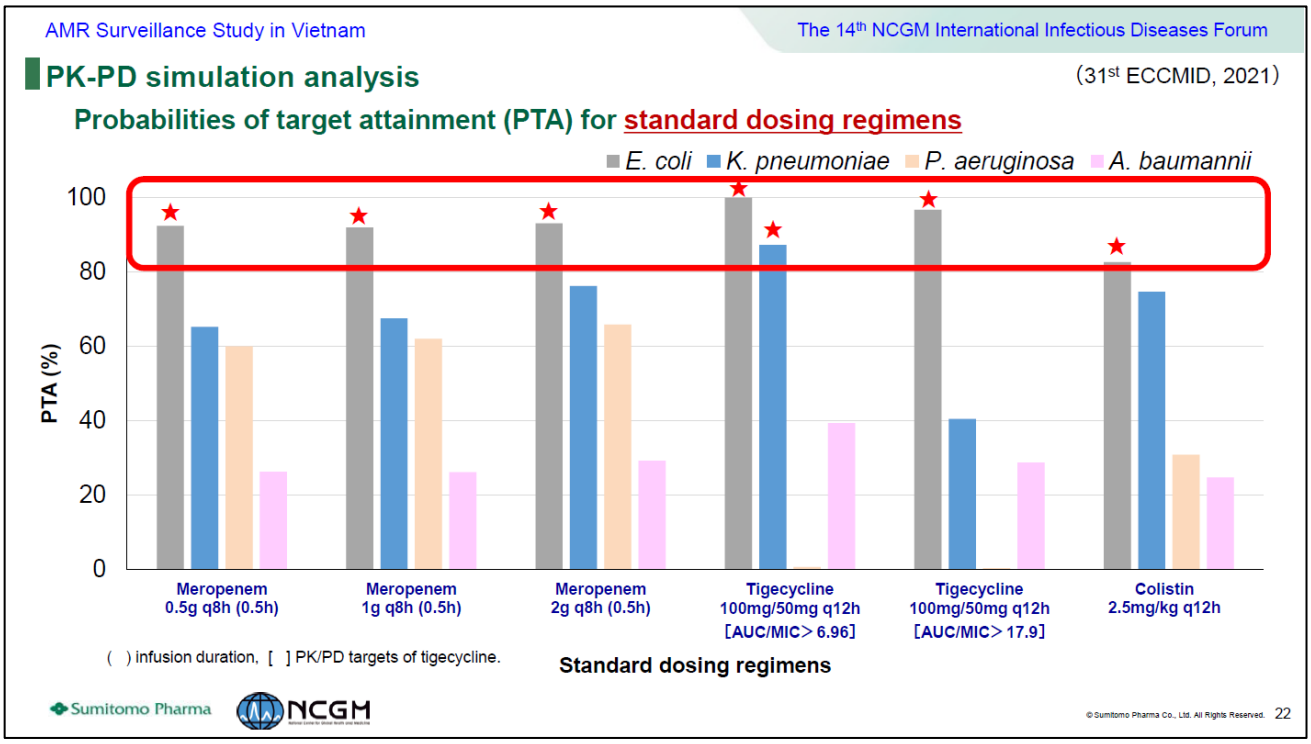
The MIC ranges, MIC_{50}, MIC_{80}, MIC_{90}, and S/I/R (%) of clinical isolates of 4 Gram-negative bacteria in Vietnam

Pathogens	Drug	MIC (μg/mL)				S/I/R (%) in CLSI			S/I/R (%) in EUCAST		
		Range	MIC_{50}	MIC_{80}	MIC_{90}	S	I	R	S	I	R
Escherichia coli (n=316)	MRP	0.015->128	0.03	0.03	0.12	91.8	0.0	8.2	91.8	0.9	7.3
	IMP	0.06->128	0.12	0.5	1	90.5	1.3	8.2	91.8	0.6	7.6
	DRP	0.015->64	0.03	0.06	0.12	91.8	0.0	8.2	91.8	0.0	8.2
	TGC	0.06-1	0.12	0.25	0.25	nd	nd	nd	99.1	-	0.9
	CLT	0.25-8	0.5	1	1	-	97.8	2.2	97.8	-	2.2
Klebsiella pneumoniae (n=324)	MRP	0.015->128	0.03	16	32	64.2	0.3	35.5	64.5	8.6	26.9
	IMP	0.06->128	0.25	8	32	62.0	2.5	35.5	64.5	7.4	28.1
	DRP	0.015->64	0.06	16	32	64.2	0.9	34.9	64.2	0.9	34.9
	TGC	0.25-8	0.5	1	1	nd	nd	nd	-	-	-
	CLT	0.25->32	0.5	1	1	-	92.9	7.1	92.9	-	7.1
Pseudomonas aeruginosa (n=294)	MRP	0.03 - >128	0.5	>128	>128	60.2	1.7	38.1	60.2	4.8	35.0
	IMP	0.12 - >128	2	>128	>128	59.2	2.0	38.8	0.0	61.2	38.8
	DRP	0.06 - >64	0.5	>64	>64	61.9	3.7	34.4	58.8	3.1	38.1
	TGC	0.25 - 128	16	32	32	nd	nd	nd	-	-	-
	CLT	0.25 - 4	1	1	1	-	99.7	0.3	99.7	-	0.3
Acinetobacter baumannii (n=299)	MRP	0.06 - 128	64	64	128	26.8	1.0	72.2	26.8	3.3	69.9
	IMP	0.06 - 128	64	64	128	26.8	0.0	73.2	26.8	0.0	73.2
	DRP	0.03 - >64	64	64	64	26.8	2.0	71.2	26.8	0.0	73.2
	TGC	0.06 - 8	2	2	2	nd	nd	nd	IE	IE	IE
	CLT	0.5 - >32	1	2	2	-	97.3	2.7	97.3	-	2.7

MRP: meropenem; IMP: imipenem; DRP: doripenem; TGC: tigecycline; CLT: colistin

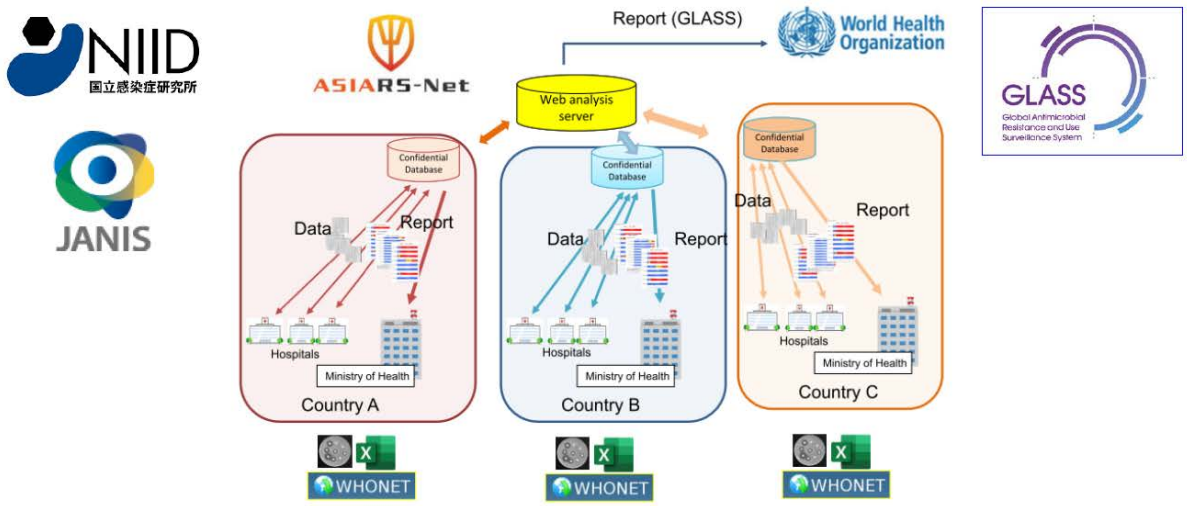
According to the study, 1280 were collected and there were overlaps or the sampling bias minimized. And also, the selection criteria were quite strict. So, in that sense, a lot of people made much effort to collect these high quality, 1263 strains which is 98.7% of the target and

one-fourth of those four strains, four species were well balanced. The CLSI and also the U.S. guidelines of this trial for E. coli was 8% or 9%. So, compared with the previous studies, it is similar. For the Klebsiella pneumoniae, it was about 27% to 35%. So, this result is similar or higher than the previous studies. For the P. aeruginosa, it was 35% to 38%, so below 40%. So, compared to the developed nations, it is low. Acinetobacter baumannii, over 70%. So, this result is feedbacked to the investigators in Vietnam. They thought that this is better than the actual, because they know the community-based, as well as the hospital-based infections. Therefore, their impression of AMR was much higher.



Various dosing regimens were broken down to look at the PTA percentage and assist practitioners to decide the therapy given. Although we don't have time to discuss this, in addition to those basic results, the latest simulation models will be brought into this program as well.

Future Plan for Global data-base (ASIARS-Net, WHONET, WHO-GLASS, etc)



https://janis.mhlw.go.jp/english/asiars-net/index.html#

Another point is the vulnerable database. This is the NIID JANIS team-provided advice. So, they have the ASIARS-Net or the ASIA JANIS, and they are kind enough to make it available for us. So, they entered into this ASIARS-Net so that the Vietnam physicians will be able to see the analyzed result. While this is a future approach, but with those databases, we would like to make patients in Vietnam be offered with evidence-based medicine. That is the final goal of Sumitomo Pharma and NCGM.

Acknowledgements for Partnership

So, I just highlighted the important points of this partnership and the many stakeholders

involved – NCGM, Sumitomo Pharma, JICA, PMDA, MHLW, Vietnam government, NIID and also PATH. Those investigators gave us valuable advice. And with their advice, this surveillance study and also the discussion of the feedback with the stakeholders is continued. do hope that we can continue to be the one team. Although we didn't have the slide, we are preparing for the second phase of the study. So, with this second phase, we will be able to continue collaborative research.

That's all. Thank you for your attention.