

### Current Progress in Dengue Vaccine Clinical Trial

Wei Chung\*, I-An Chen, Jen-Ron Chiang

#### Abstract

Dengue is one of the most important vector-borne viral diseases. Global phenomena such as urbanization and international travel are key factors in facilitating the spread of dengue causing major public health problems worldwide. There are four serotypes of dengue viruses (DENV), each serotype of DENV is capable of causing self-limited dengue fever (DF) or dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) by a relatively high mortality rate and/or high sequelae rate in survivors. No cure for dengue exists; treatment is limited to rehydration therapy, and with vector control strategies proving to be relatively ineffective. Moreover dengue life cycles are maintained between arthropod vectors and amplifying/reservoir hosts in the absence of humans, eradication of dengue might be extremely difficult. So vaccine development is considered a reasonable method to prevent dengue infections. In this article, we summarize the current dengue vaccine candidates in clinical trials, and discuss the directions and problems in vaccines development.

**Keywords:** Dengue ; tetravalent ; vaccine introduction.

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## Review of Tetanus Vaccine

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### Abstract

Tetanus is a disease caused by *Clostridium tetani*, and was first described by Hippocrates in 400 BC. The mortality rate was high until tetanus toxoid was invented in 1924. The policy of fully vaccination was started in 1956 in Taiwan, and the annual reported cases are about 20 cases in recent years. According to the estimation by WHO in 2008, there are more than 50,000 neonatal deaths due to tetanus. Though a 92% reduction compared to 1980s, it is still an important public health issue in poor and undeveloped countries. In the past decade there was no neonatal tetanus case in Taiwan. Our epidemic prevention strategies are maintaining and elevating vaccination rates, ensuring the supply of vaccines, and enhancing the hygiene conception of citizens in the future.

**Keywords:** tetanus ; tetanus toxoid ; neonatal tetanus ; adjuvant

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Weekly Data of Notifiable Infectious Diseases (by week of diagnosis)

Case diagnosis week		Week 14		Week 1–14	
Classification	Disease Diagnosed <sup>1</sup>	2015	2014	2015	2014
Category I	Plague	0	0	0	0
	Rabies	0	0	0	0
	SARS	0	0	0	0
	Smallpox	0	0	0	0
Category II	Acute Flaccid Paralysis	1	0	5	10
	Acute Viral Hepatitis type A	1	2	24	45
	Amoebiasis	7	2	95	63
	Anthrax	0	0	0	0
	Chikungunya Fever	0	0	3	4
	Cholera	0	0	0	0
	Dengue Fever	9	2	177	105
	Dengue Hemorrhagic Fever/Dengue Shock Syndrome	0	0	0	4
	Diphtheria	0	0	0	0
	Enterohemorrhagic E. coli Infection	0	0	0	0
	Epidemic Typhus Fever	0	0	0	0
	Hantavirus Pulmonary Syndrome	0	0	0	0
	Hemorrhagic Fever with Renal Syndrome	0	0	0	1
	Malaria	0	0	3	4
	Measles	0	0	1	6
	Meningococcal Meningitis	0	0	1	2
	Paratyphoid Fever	0	0	1	4
	Poliomyelitis	0	0	0	0
	Rubella	1	0	3	3
Shigellosis	3	3	63	45	
Typhoid fever	2	0	12	8	
West Nile Fever	0	0	0	0	
Category III	Acute Viral Hepatitis type B	4	3	30	22
	Acute Viral Hepatitis type C <sup>5</sup>	6	3	53	33
	Acute Viral Hepatitis type D	0	0	1	0
	Acute Viral Hepatitis type E	0	0	1	4
	Acute Viral Hepatitis untype	0	0	0	1
	Congenital Rubella Syndrome	0	0	0	0
	Enteroviruses Infection with Severe Complications	0	0	1	1
	Haemophilus Influenza type b Infection	0	1	1	1
	Japanese Encephalitis	0	0	0	0
	Legionellosis	1	2	40	35
	Mumps <sup>2</sup>	15	13	190	197
	Neonatal Tetanus	0	0	0	0
	Pertussis	0	1	33	6
	Tetanus <sup>2</sup>	0	0	1	1
Category IV	Botulism	0	0	1	0
	Brucellosis	0	0	0	0
	Complicated Influenza	26	30	271	1375
	Complicated Varicella <sup>4</sup>	0	2	19	25
	Endemic Typhus Fever	0	0	0	5
	Herpesvirus B Infection	0	0	0	0
	Invasive Pneumococcal Disease	12	20	200	253
	Leptospirosis	0	0	10	11
	Lyme Disease	0	0	0	0
	Melioidosis	1	1	6	7
	Q Fever	0	0	7	18
	Scrub Typhus	2	0	59	69
	Toxoplasmosis	1	0	1	3
Tularremia	0	0	0	0	
Category V	Ebola Virus Disease	0	0	0	0
	Ebola-Marburg Hemorrhagic Fever	0	0	0	0
	Novel Influenza A Virus Infections <sup>6</sup>	0	0	0	0
	Lassa Fever	0	0	0	0
	Rift Valley Fever	0	0	0	0
	Middle East Respiratory Syndrome Coronavirus	0	0	0	0
Yellow Fever	0	0	0	0	

1. The following 8 chronic diseases are excluded from the table: MDR-TB, Tuberculosis, Syphilis, Gonorrhea, HIV Infection, AIDS, Hansen Disease and Creutzfeldt-Jakob Disease.
2. Reported cases.
3. The epidemiological week calendar established by the World Health Organization is adopted for calculating each week's cumulative total.
4. Since 2014/1/1, "Varicella" was modified to "Complicated Varicella".
5. Since 2014/3/6, the case definition for confirmed Acute hepatitis C was changed from "meet the clinical and laboratory conditions" to "meet the clinical or laboratory conditions".
6. Since 2014/7/1, various subtypes of human cases of avian influenza are reported as "novel influenza A virus infections", a Category V Notifiable Infectious Disease. The original "H5N1 flu" and "H7N9 flu", which were respectively listed as a Category I Notifiable Infectious Disease and a Category V Notifiable Infectious Disease were removed from the list on the same day.

### Suspected Clusters

- Thirteen clusters were reported, including 5 upper respiratory tract infection clusters, 4 tuberculosis clusters, 2 influenza-like illness clusters, 1 diarrhea cluster and 1 varicella cluster.

### Imported Infectious Diseases

- 14 confirmed cases were imported from 4 countries during week 14 of 2015.

<b>Country</b> <b>Disease</b>	<b>Indonesia</b>	<b>China</b>	<b>Vietnam</b>	<b>Malaysia</b>	<b>Total</b>
<b>Dengue Fever</b>	4		1	1	6
<b>Amoebiasis</b>	4				4
<b>Typhoid fever</b>	2				2
<b>Rubella</b>		1			1
<b>Shigellosis</b>	1				1
<b>Total</b>	11	1	1	1	14

Note: The statistics listed in this table include imported cases that were either confirmed or updated\* in the previous week.

- A total of 194 confirmed cases were imported from 23 countries in 2015.
- Top 3 imported diseases : Dengue fever (64), Amoebiasis (57), Shigellosis (35).
- Top 3 countries responsible for most imported cases : Indonesia (128), Philippines (10), Vietnam (10).

### Summary of Epidemic

- **Influenza** : The influenza activity still remained high. Since January 1, 2015, a cumulative total of 272 cases of severe complicated influenza have been confirmed, including 46 cases infected by H1N1, 193 cases infected by H3N2, 4 cases infected by untyped influenza A and 29 cases infected by influenza B. Among these cases, 34 deaths were caused by infection with H3N2, 3 deaths were caused by infection with H1N1 and 1 death was caused by infection with influenza B. During week 14, H3N2 was the dominant strain circulating in the community and followed by influenza B, which became more active. Thus far, no resistant viruses have been detected.

- **Dengue fever** : New sporadic cases have been reported in Sanmin District and Niasong District, Kaohsiung City. Taiwan CDC will continue to monitor the development of the epidemic. The interval between the date of symptoms onset and the date of notification of confirmed cases recently were longer. The public is urged to seek medical attention immediately if suspected symptoms develop. Doctors are advised to stay vigilant for and to ensure prompt case reporting. The number of imported dengue fever cases reported last week is higher than those reported during the same period in the past five years. Most of our imported cases came from countries in Southeast Asia.
  
- **Enterovirus** : The ER consultation rate for enterovirus infection has slightly exceeded the epidemic threshold. Coxsackie A virus is currently the dominant strain circulating in the community.

## Weekly Data of Notifiable Infectious Diseases (by week of diagnosis)

Case diagnosis week		Week 15		Week 1—15	
Classification	Disease Diagnosed <sup>1</sup>	2015	2014	2015	2014
Category I	Plague	0	0	0	0
	Rabies	0	0	0	0
	SARS	0	0	0	0
	Smallpox	0	0	0	0
Category II	Acute Flaccid Paralysis	1	1	6	11
	Acute Viral Hepatitis type A	0	3	24	48
	Amoebiasis	4	7	99	70
	Anthrax	0	0	0	0
	Chikungunya Fever	0	1	3	5
	Cholera	0	0	0	0
	Dengue Fever	4	1	181	106
	Dengue Hemorrhagic Fever/Dengue Shock Syndrome	0	0	0	4
	Diphtheria	0	0	0	0
	Enterohemorrhagic E. coli Infection	0	0	0	0
	Epidemic Typhus Fever	0	0	0	0
	Hantavirus Pulmonary Syndrome	0	0	0	0
	Hemorrhagic Fever with Renal Syndrome	0	0	0	1
	Malaria	0	1	3	5
	Measles	0	2	1	8
	Meningococcal Meningitis	0	0	1	2
	Paratyphoid Fever	0	2	1	6
	Poliomyelitis	0	0	0	0
	Rubella	0	0	3	3
	Shigellosis	3	1	66	46
Typhoid fever	0	0	12	8	
West Nile Fever	0	0	0	0	
Category III	Acute Viral Hepatitis type B	2	1	32	23
	Acute Viral Hepatitis type C <sup>5</sup>	5	9	58	42
	Acute Viral Hepatitis type D	0	0	1	0
	Acute Viral Hepatitis type E	0	1	1	5
	Acute Viral Hepatitis untype	0	0	0	1
	Congenital Rubella Syndrome	0	0	0	0
	Enteroviruses Infection with Severe Complications	0	0	1	1
	Haemophilus Influenza type b Infection	0	0	1	1
	Japanese Encephalitis	0	0	0	0
	Legionellosis	2	0	42	35
	Mumps <sup>2</sup>	21	17	211	214
	Neonatal Tetanus	0	0	0	0
	Pertussis	3	4	36	10
	Tetanus <sup>2</sup>	0	0	1	1
Category IV	Botulism	0	0	1	0
	Brucellosis	0	0	0	0
	Complicated Influenza	27	45	298	1420
	Complicated Varicella <sup>4</sup>	1	0	20	25
	Endemic Typhus Fever	1	0	1	5
	Herpesvirus B Infection	0	0	0	0
	Invasive Pneumococcal Disease	8	16	208	269
	Leptospirosis	1	1	11	12
	Lyme Disease	0	0	0	0
	Melioidosis	0	0	6	7
	Q Fever	1	0	8	18
	Scrub Typhus	3	0	62	69
	Toxoplasmosis	0	2	1	5
Tularremia	0	0	0	0	
Category V	Ebola Virus Disease	0	0	0	0
	Ebola-Marburg Hemorrhagic Fever	0	0	0	0
	Novel Influenza A Virus Infections <sup>6</sup>	0	0	0	0
	Lassa Fever	0	0	0	0
	Rift Valley Fever	0	0	0	0
	Middle East Respiratory Syndrome Coronavirus	0	0	0	0
Yellow Fever	0	0	0	0	

1. The following 8 chronic diseases are excluded from the table: MDR-TB, Tuberculosis, Syphilis, Gonorrhoea, HIV Infection, AIDS, Hansen Disease and Creutzfeldt-Jakob Disease.  
2. Reported cases.  
3. The epidemiological week calendar established by the World Health Organization is adopted for calculating each week's cumulative total.  
4. Since 2014/1/1, "Varicella" was modified to "Complicated Varicella".  
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6. Since 2014/7/1, various subtypes of human cases of avian influenza are reported as "novel influenza A virus infections", a Category V Notifiable Infectious Disease. The original "H5N1 flu" and "H7N9 flu", which were respectively listed as a Category I Notifiable Infectious Disease and a Category V Notifiable Infectious Disease were removed from the list on the same day.

### Suspected Clusters

- Twenty-three clusters were reported, including 3 tuberculosis clusters, 9 diarrhea clusters, 5 upper respiratory tract infection clusters, 3 influenza-like illness clusters, and 3 varicella clusters.

### Imported Infectious Diseases

- 10 confirmed cases were imported from 4 countries during week 15 of 2015.

Country \ Disease	Indonesia	Philippines	Vietnam	Malaysia	Total
Amoebiasis	2	1	1		4
Dengue Fever	3				3
Shigellosis	2				2
Malaria				1	1
<b>Total</b>	7	1	1	1	10

Note: The statistics listed in this table include imported cases that were either confirmed or updated\* in the previous week.

- A total of 203 confirmed cases were imported from 23 countries in 2015.
- Top 3 imported diseases : Dengue fever (66), Amoebiasis (61), Shigellosis (37).
- Top 3 countries responsible for most imported cases : Indonesia (134), Vietnam (11), Philippines (11).

### Summary of Epidemic

- **Influenza** : The influenza activity gradually slowed down. Since January 1, 2015, a total number of 298 cases of severe complicated influenza have been confirmed, including 52 cases infected by H1N1, 209 cases infected by H3N2, 4 cases infected by untyped influenza A and 33 cases infected by influenza B. Among these cases, 36 deaths were caused by infection with H3N2, 3 deaths were caused by infection with H1N1 and 3 deaths were caused by infection with influenza B. During week 15, H3N2 was the dominant strain circulating in the community and followed by influenza B, which became more active. Thus far, no resistant viruses have been detected.
- **Dengue Fever** : New sporadic cases were reported in Kaohsiung City. The interval between the date of symptom onset and the date of reporting of confirmed cases recently has been longer. In some cases, the interval from symptom onset to seeking first medical treatment is up to five days and a case is only reported after seeking to 3-4 times of medical assistance. The public is urged to seek medical attention immediately if suspected symptoms develop. Doctors are advised to stay vigilant for and to ensure prompt case reporting.

- **Enterovirus** : The ER consultation rate for enterovirus infection has fluctuated around the epidemic threshold. Coxsackie A virus is currently the dominant strain circulating in the community. This year, a total of one case of severe cases of enterovirus has been confirmed (CB5).

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