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疫情報導
TAIWAN EPIDEMIOLOGY BULLETIN
November 7, 2023 Vol.39 No.21
Original Article

# Application of Advanced Whole Genome Sequencing Technology for Tuberculosis Outbreak Investigation

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**Abstract**

Tuberculosis (TB) is an *aerosol-transmissible* disease caused by the *Mycobacterium tuberculosis* complex. Blocking the transmission chain is one of the key strategies to stop TB. The global tuberculosis control has entered the genomic era. For facilitating TB control, we used whole genome sequencing (WGS) to obtain single nucleotide polymorphism (SNP) information of *M. tuberculosis* to improve discriminative limitations of conventional genotyping methods and to strengthen the delineation of transmission networks. Based on a confirmed multidrug-resistant TB (MDR-TB) outbreak, we define SNPs differences for TB outbreak investigations. To confirm an outbreak, the transmission events between cases within clusters were calculated using thresholds of ≤ 5 (definite) and ≤ 15 (probable) SNPs difference between isolates. Depending on cost-effectiveness, an algorithm was established using mycobacterial interspersed repetitive units-variable number tandem repeat (MIRU-VNTR) and WGS as the primary and secondary genotyping, respectively. However, WGS still needs to be combined with classical epidemiological methods to improve outbreak investigations.

**Keywords:** Tuberculosis, *Mycobacterium tuberculosis* complex, whole genome sequencing, outbreak investigation

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Received: Apr. 29, 2021
DOI: 10.6525/TEB.202311_39(21).0001
Accepted: Sep. 16, 2021

# week 42–week 43, 2023 (Oct. 15, 2023–Oct. 28, 2023)

DOI: 10.6525/TEB.202311_39(21).0002

## Weekly Data of Notifiable Inases (by week of diagnosis)

| Case diagnosis year | | Week 42★ | | Week 1-42 | | | |
|---|---|---|---|---|---|---|---|
| | | | | 2023 | | 2022 | |
| Classification | Disease Diagnosed | 2023 | 2022 | Total cases★ | Imported cases | Total cases★ | Imported cases |
| Category I | Plague | 0 | 0 | 0 | 0 | 0 | 0 |
| | Rabies | 0 | 0 | 0 | 0 | 0 | 0 |
| | SARS | 0 | 0 | 0 | 0 | 0 | 0 |
| | Smallpox | 0 | 0 | 0 | 0 | 0 | 0 |
| Category II | Cholera | 0 | 0 | 1 | 0 | 0 | 0 |
| | Typhoid fever | 0 | 0 | 8 | 6 | 3 | 1 |
| | Paratyphoid Fever | 0 | 0 | 13 | 1 | 0 | 0 |
| | Epidemic Typhus Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Shigellosis | 2 | 0 | 55 | 12 | 59 | 5 |
| | Amoebiasis | 3 | 4 | 224 | 89 | 168 | 58 |
| | Enterohemorrhagic E.coli Infection | 0 | 0 | 0 | 0 | 2 | 0 |
| | Anthrax | 0 | 0 | 0 | 0 | 0 | 0 |
| | Diphtheria | 0 | 0 | 0 | 0 | 0 | 0 |
| | Meningococcal Meningitis | 0 | 0 | 3 | 0 | 1 | 0 |
| | Poliomyelitis | 0 | 0 | 0 | 0 | 0 | 0 |
| | Acute Flaccid Paralysis | 2 | 1 | 48 | 0 | 23 | 0 |
| | Measles | 0 | 0 | 2 | 2 | 1 | 0 |
| | Rubella | 0 | 0 | 0 | 0 | 0 | 0 |
| | Dengue Fever | 1,776 | 3 | 18,706 | 201 | 66 | 46 |
| | West Nile Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Acute Viral Hepatitis type A | 3 | 0 | 73 | 4 | 114 | 1 |
| | Malaria | 0 | 0 | 1 | 1 | 2 | 2 |
| | Chikungunya Fever | 0 | 0 | 8 | 8 | 1 | 1 |
| | Hantavirus syndrome | 0 | 0 | 6 | 0 | 3 | 0 |
| | Zika virus infection | 0 | 0 | 3 | 3 | 0 | 0 |
| | Mpox | 3 | 0 | 345 | 13 | 4 | 4 |
| Category III | Acute Viral Hepatitis type B | 4 | 2 | 110 | 6 | 81 | 0 |
| | Acute Viral Hepatitis type C | 8 | 13 | 423 | 1 | 385 | 2 |
| | Acute Viral Hepatitis type D | 0 | 0 | 0 | 0 | 0 | 0 |
| | Acute Viral Hepatitis type E | 0 | 0 | 12 | 4 | 10 | 0 |
| | Acute Viral Hepatitis, untyped | 0 | 0 | 9 | 1 | 0 | 0 |
| | Congenital Syphilis | 0 | 0 | 0 | 0 | 0 | 0 |
| | Congenital Rubella Syndrome | 0 | 0 | 0 | 0 | 0 | 0 |
| | Enteroviruses Infection with Severe Complications | 0 | 0 | 13 | 0 | 0 | 0 |
| | Haemophilus Influenza type b Infection | 0 | 0 | 1 | 0 | 2 | 0 |
| | Japanese Encephalitis | 0 | 0 | 23 | 0 | 19 | 0 |
| | Legionnaires' Disease | 6 | 3 | 318 | 8 | 263 | 1 |
| | Mumps | 6 | 7 | 230 | 7 | 195 | 0 |
| | Neonatal Tetanus | 0 | 0 | 0 | 0 | 0 | 0 |
| | Pertussis | 0 | 1 | 0 | 0 | 1 | 0 |
| | Tetanus | 0 | 0 | 5 | 0 | 7 | 0 |
| Category IV | Botulism | 0 | 0 | 0 | 0 | 0 | 0 |
| | Brucellosis | 0 | 0 | 0 | 0 | 0 | 0 |
| | Complicated Varicella | 0 | 0 | 36 | 0 | 26 | 0 |
| | Endemic Typhus Fever | 1 | 0 | 22 | 0 | 11 | 0 |
| | Herpesvirus B Infection | 0 | 0 | 0 | 0 | 0 | 0 |
| | Influenza Case with Severe Complications | 25 | 0 | 857 | 11 | 1 | 0 |
| | Invasive Pneumococcal Disease | 3 | 6 | 225 | 1 | 146 | 0 |
| | Leptospirosis | 3 | 8 | 62 | 0 | 54 | 0 |
| | Listeriosis | 0 | 5 | 157 | 2 | 119 | 0 |
| | Lyme Disease | 0 | 0 | 0 | 0 | 1 | 1 |
| | Melioidosis | 1 | 1 | 19 | 2 | 19 | 2 |
| | Q Fever | 0 | 0 | 3 | 0 | 3 | 0 |
| | Scrub Typhus | 13 | 7 | 162 | 0 | 233 | 0 |
| | Toxoplasmosis | 0 | 0 | 23 | 2 | 20 | 0 |
| | Tularemia | 0 | 0 | 0 | 0 | 0 | 0 |
| | Severe Fever with Thrombocytopenia Syndrome | 0 | 0 | 0 | 0 | 1 | 0 |
| | Severe Pneumonia with Novel Pathogens | 288 | 266,230 | 1,393,788 | 18,137 | 7,433,034 | 33,637 |
| Category V | Ebola Virus Disease | 0 | 0 | 0 | 0 | 0 | 0 |
| | Lassa Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Marburg Hemorrhagic Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Middle East Respiratory Syndrome Coronavirus Infections | 0 | 0 | 0 | 0 | 0 | 0 |
| | Novel Influenza A Virus Infections | 0 | 0 | 1 | 0 | 0 | 0 |
| | Rift Valley Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Yellow Fever | 0 | 0 | 0 | 0 | 0 | 0 |

1. ★The weekly and cumulative total numbers include indigenous and imported cases of notifiable infectious diseases.
2. MDR-TB, Tuberculosis, Syphilis, Gonorrhea, HIV Infection, AIDS, Hansen's Disease and Creutzfeldt-Jakob Disease are excluded from the table.
3. Numbers of Mumps and Tetanus are based on reported cases and summed up by week of report.
4. "Mpox" has been listed as a Notifiable Infectious Disease since June 23, 2022.
5. "Severe Pneumonia with Novel Pathogens": The case definition has been revised to include patients who have both a positive test for SARS-CoV-2 and associated complications since March 20, 2023. Additionally, it has been modified from Category V to Category IV since May 1, 2023.

## Suspected Clusters

●Fifty-one clusters related to Upper respiratory tract infection (32), Diarrhea (12), Enterovirus (3), TB (2) and Varicella (2) were reported during week 42.

## Imported Infectious Diseases

●There were 15 imported cases from at least 6 countries / areas during week 42.
**Dengue Fever**：12 cases from Vietnam (8), India (2), Indonesia (1), and Cambodia (1).
**Severe Pneumonia with Novel Pathogens**：2 cases from China (1), and Japan (1).
**Amoebiasis**：1 case from Vietnam.

●During week 1-42, there were 18,522 imported cases of notifiable diseases. The top three were Severe Pneumonia with Novel Pathogens (18,137), Dengue Fever (201) and Amoebiasis (89).

●During week 1-42, imported cases of notifiable diseases were from at least 48 countries/areas. The top three were China (3,179), Japan (728) and Thailand (206).

## Summary of Epidemic

●**Influenza:** In the midst of the epidemic period, the epidemic has decreased recently.

●**Enterovirus**: The epidemic has decreased.

●**Dengue Fever:** The epidemic is similar to the previous week, the risk of transmission remains high.

## Weekly Data of Notifiable Inases (by week of diagnosis)

| Case diagnosis year | | Week 43 | | Week 1-43 | | | |
|---|---|---|---|---|---|---|---|
| | | | | 2023 | | 2022 | |
| Classification | Disease Diagnosed | 2023 | 2022 | Total cases★ | Imported cases | Total cases★ | Imported cases |
| Category I | Plague | 0 | 0 | 0 | 0 | 0 | 0 |
| | Rabies | 0 | 0 | 0 | 0 | 0 | 0 |
| | SARS | 0 | 0 | 0 | 0 | 0 | 0 |
| | Smallpox | 0 | 0 | 0 | 0 | 0 | 0 |
| Category II | Cholera | 0 | 0 | 1 | 0 | 0 | 0 |
| | Typhoid fever | 0 | 0 | 8 | 6 | 3 | 1 |
| | Paratyphoid Fever | 0 | 3 | 13 | 1 | 3 | 0 |
| | Epidemic Typhus Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Shigellosis | 0 | 1 | 55 | 12 | 60 | 5 |
| | Amoebiasis | 2 | 5 | 226 | 91 | 173 | 59 |
| | Enterohemorrhagic E.coli Infection | 0 | 0 | 0 | 0 | 2 | 0 |
| | Anthrax | 0 | 0 | 0 | 0 | 0 | 0 |
| | Diphtheria | 0 | 0 | 0 | 0 | 0 | 0 |
| | Meningococcal Meningitis | 0 | 0 | 3 | 0 | 1 | 0 |
| | Poliomyelitis | 0 | 0 | 0 | 0 | 0 | 0 |
| | Acute Flaccid Paralysis | 2 | 0 | 50 | 0 | 23 | 0 |
| | Measles | 0 | 0 | 2 | 2 | 1 | 0 |
| | Rubella | 0 | 0 | 0 | 0 | 0 | 0 |
| | Dengue Fever | 1,525 | 4 | 20,230 | 210 | 70 | 50 |
| | West Nile Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Acute Viral Hepatitis type A | 2 | 0 | 75 | 5 | 114 | 1 |
| | Malaria | 0 | 0 | 1 | 1 | 2 | 2 |
| | Chikungunya Fever | 0 | 0 | 8 | 8 | 1 | 1 |
| | Hantavirus syndrome | 0 | 0 | 6 | 0 | 3 | 0 |
| | Zika virus infection | 0 | 0 | 3 | 3 | 0 | 0 |
| | Mpox | 5 | 0 | 350 | 13 | 4 | 4 |
| Category III | Acute Viral Hepatitis type B | 3 | 4 | 113 | 6 | 85 | 0 |
| | Acute Viral Hepatitis type C | 8 | 8 | 431 | 1 | 393 | 2 |
| | Acute Viral Hepatitis type D | 0 | 0 | 0 | 0 | 0 | 0 |
| | Acute Viral Hepatitis type E | 0 | 0 | 12 | 4 | 10 | 0 |
| | Acute Viral Hepatitis, untyped | 0 | 0 | 9 | 1 | 0 | 0 |
| | Congenital Syphilis | 0 | 0 | 0 | 0 | 0 | 0 |
| | Congenital Rubella Syndrome | 0 | 0 | 0 | 0 | 0 | 0 |
| | Enteroviruses Infection with Severe Complications | 0 | 0 | 13 | 0 | 0 | 0 |
| | Haemophilus Influenza type b Infection | 0 | 0 | 1 | 0 | 2 | 0 |
| | Japanese Encephalitis | 1 | 0 | 24 | 0 | 19 | 0 |
| | Legionnaires' Disease | 6 | 9 | 324 | 8 | 272 | 1 |
| | Mumps | 9 | 17 | 239 | 7 | 212 | 0 |
| | Neonatal Tetanus | 0 | 0 | 0 | 0 | 0 | 0 |
| | Pertussis | 0 | 0 | 0 | 0 | 1 | 0 |
| | Tetanus | 0 | 0 | 5 | 0 | 7 | 0 |
| Category IV | Botulism | 0 | 0 | 0 | 0 | 0 | 0 |
| | Brucellosis | 0 | 0 | 0 | 0 | 0 | 0 |
| | Complicated Varicella | 2 | 2 | 38 | 0 | 28 | 0 |
| | Endemic Typhus Fever | 1 | 0 | 23 | 0 | 11 | 0 |
| | Herpesvirus B Infection | 0 | 0 | 0 | 0 | 0 | 0 |
| | Influenza Case with Severe Complications | 18 | 0 | 875 | 11 | 1 | 0 |
| | Invasive Pneumococcal Disease | 3 | 2 | 228 | 1 | 148 | 0 |
| | Leptospirosis | 1 | 0 | 63 | 0 | 54 | 0 |
| | Listeriosis | 5 | 1 | 162 | 2 | 120 | 0 |
| | Lyme Disease | 0 | 0 | 0 | 0 | 1 | 1 |
| | Melioidosis | 1 | 1 | 20 | 2 | 20 | 2 |
| | Q Fever | 0 | 0 | 3 | 0 | 3 | 0 |
| | Scrub Typhus | 6 | 7 | 168 | 0 | 240 | 0 |
| | Toxoplasmosis | 0 | 1 | 23 | 2 | 21 | 0 |
| | Tularemia | 0 | 0 | 0 | 0 | 0 | 0 |
| | Severe Fever with Thrombocytopenia Syndrome | 0 | 0 | 0 | 0 | 1 | 0 |
| | Severe Pneumonia with Novel Pathogens | 225 | 239,986 | 1,394,013 | 18,138 | 7,673,020 | 33,935 |
| Category V | Ebola Virus Disease | 0 | 0 | 0 | 0 | 0 | 0 |
| | Lassa Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Marburg Hemorrhagic Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Middle East Respiratory Syndrome Coronavirus Infections | 0 | 0 | 0 | 0 | 0 | 0 |
| | Novel Influenza A Virus Infections | 0 | 0 | 1 | 0 | 0 | 0 |
| | Rift Valley Fever | 0 | 0 | 0 | 0 | 0 | 0 |
| | Yellow Fever | 0 | 0 | 0 | 0 | 0 | 0 |

1. ★The weekly and cumulative total numbers include indigenous and imported cases of notifiable infectious diseases.
2. MDR-TB, Tuberculosis, Syphilis, Gonorrhea, HIV Infection, AIDS, Hansen's Disease and Creutzfeldt-Jakob Disease are excluded from the table.
3. Numbers of mumps and tetanus cases are summed up by the week of report.
4. "Mpox" has been listed as a Notifiable Infectious Disease since June 23, 2022.
5. "Severe Pneumonia with Novel Pathogens": The case definition has been revised to include patients who have both a positive test for SARS-CoV-2 and associated complications since March 20, 2023. Additionally, it has been modified from Category V to Category IV since May 1, 2023.

## Suspected Clusters

●Fifty-seven clusters related to Upper respiratory tract infection (36), Diarrhea (14), TB (6), and Enterovirus (1) were reported during week 43.

## Imported Infectious Diseases

●There were 15 imported cases from at least 5 countries / areas during week 43.

**Dengue Fever**：12 cases from Vietnam (7), Thailand (4), and Indonesia (1).

**Severe Pneumonia with Novel Pathogens**：1 case from Turkey.

**Acute Viral Hepatitis type A**：1 case from USA.

**Amoebiasis**：1 case from Indonesia.

●During week 1-43, there were 18,535 imported cases of notifiable diseases. The top three were Severe Pneumonia with Novel Pathogens (18,138), Dengue Fever (210), Amoebiasis (91).

●During week 1-43, imported cases of notifiable diseases were from at least 48 countries/areas. The top three China (3,178), Japan (728), Thailand (209).

## Summary of Epidemic

●**Influenza:** The epidemic has decreased recently.

●**Dengue Fever:** The epidemic has decreased, but the risk of transmission remains high.

The Taiwan Epidemiology Bulletin series of publications is published by Centers for Disease Control, Ministry of Health and Welfare, Taiwan (R.O.C.) since Dec. 15, 1984.
**Publisher:** Jen-Hsiang Chuang
**Editor-in-Chief:** Yung-Ching Lin
**Executive Editor:** Hsueh-Ju Chen, Hsin-Lun Lee
**Address:** No.6, Linsen S. Rd, Jhongjheng District, Taipei City 10050, Taiwan (R.O.C.)
**Telephone No:** +886-2-2395-9825 **Website:** https://www.cdc.gov.tw/En
**Suggested Citation**:
[Author].[Article title].Taiwan Epidemiol Bull 2023;39:[inclusive page numbers]. [DOI]