National Diphtheria outbreak 2024/5

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Diphtheria

- Highly contagious and vaccine preventable
- Respiratory diphtheria illness
  - Caused by toxin producing strains of *Corynebacterium diphtheriae*
    - rarely *C. ulcerans* or *C. pseudotuberculosis*
  - **Toxin is responsible for pathogenesis and clinical presentation (and deaths) of diphtheria**
- Toxin-producing strains can cause skin lesions and may be a reservoir of infection

Infection

High index of suspicion:
sore throat + adherent membrane

- **Low grade fever**
- **Sore throat**
- **Pseudomembrane**
  - Local toxin production
  - Anywhere from nose to tracheobronchial tree
  - Dense, adherent
  - Airway obstruction
- **Cervical LAD – ‘Bull’ neck**

Differential diagnosis

Tonsilitis Diphtheria

Differential diagnoses for white patch on the throat

Vaccination for asymptomatic contacts-booster vaccine,

Differential diagnosis	Clinical feature
Infectious mononucleosis	Fever, pharyngitis, adenitis, hepatosplenomegaly, atypical lymphocytosis (splenomegaly is an important finding)
Group A streptococcal pharyngitis	Fever, absence of cough, presence of tonsillar exudates, follicles, tender jugulodigastric nodes
Diphtheria	Spots of gray and white exudate → 1/3 coalescing pseudomembrane, tightly adherent which can obstruct the respiratory tract → stridor may ensue, leading to respiratory insufficiency, suffocation
Vincent's angina	Sudden onset of painful, bleeding gums, blunting of interdental papillae, and an ulcerative necrotic slough of the gingiva
Oral candidiasis	
Tonsillar malignancy	

Systemic effects of the toxin

DAT saves lives

- **Cardiac**
  - Myocarditis - Up to 60%, 7-14 days after respiratory symptoms
  - Heart block
- **Renal failure**
- **Neurological** related to the severity of the respiratory infection)
  - 3-6 weeks - **Cranial nerve deficits** including oculomotor, ciliary paralysis, facial, and pharyngeal, or laryngeal nervous dysfunction
  - Occasionally, a stocking and glove **peripheral sensory neuropathy** .
  - 8 weeks - **Peripheral neuritis** develops 10 days to 3 months after the onset of pharyngeal disease.
    - initially as a motor defect of the proximal muscle groups in the extremities extending distally.
- **Invasive disease** may manifest in multiple organ system disease, though this is rare (non- toxigenic)

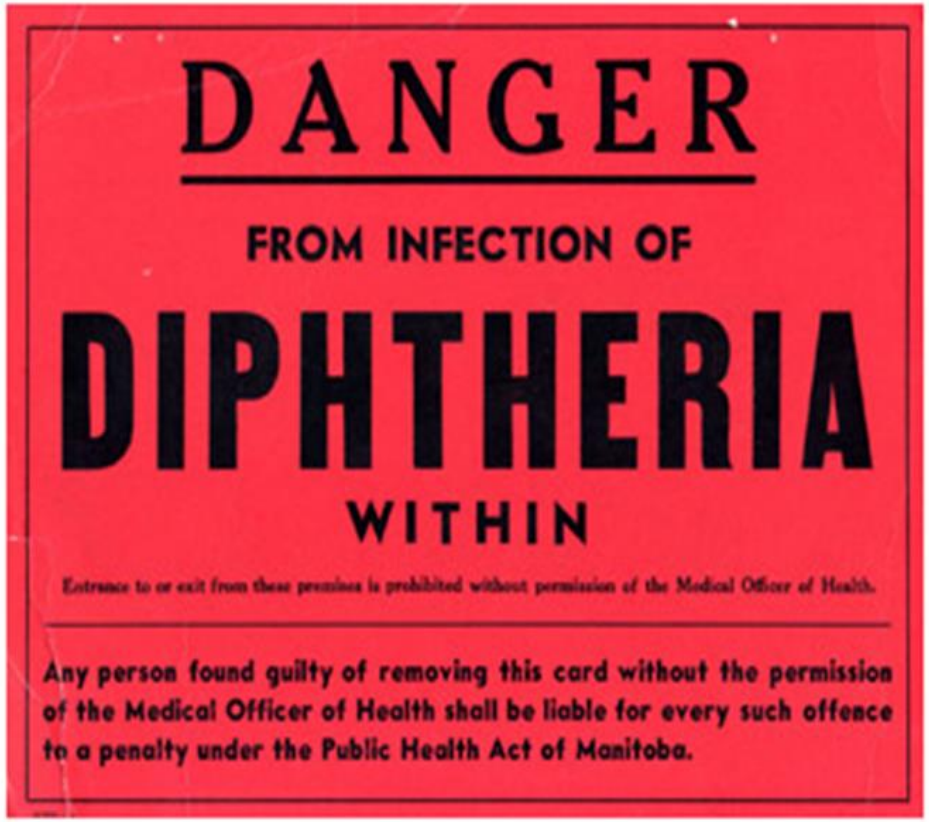
Skin disease

Fig. 1: skin ulcer covered by a yellowish membrane on leg of patient with *Corynebacterium ulcerans* infection.

Diphtheria is occasionally seen in the female genital tract, conjunctivae, or ear.

Management

Stay calm. Protect yourself. Protect other staff and patients.



Whenever you isolate a patient – remember to de-isolate!

Treatment of cases

High index of suspicion:
sore throat + adherent membrane

Components of care:

1. IPC
2. Patient management:
    1. **Manage the airway**
    2. Manage in monitored setting/HCU
    3. Antibiotics: prevent further bacterial growth
    4. **Diphtheria antitoxin (DAT): neutralize unbound toxin. DAT saves lives**
    5. Monitoring & supportive care: airway, myocarditis
3. Public & occupational health response (before lab results)

Multidisciplinary approach:

- Notifiable condition! Notify on NMC app within 24h
- Phone CDCC
- **Discuss with Infectious Diseases/NICD hotline**

- ***Team effort*** *– EM, clinicians, public health, microbiologists ,pharmacy, hospital management, IPC, ENT specialists, ID specialists, nephrology, cardiology, community workers …*

Antibiotics

Airway management

Monitoring
ECG early and repeat
U &E for kidney function
FBC to watch Hb and WCC

- Give alongside DAT (antitoxin). Do not delay!

- Firstline option:
  - Azithromycin 10mg/kg/d (max 500mg/d) IV if difficulty swallowing, then switch to oral
  - 14 days (can this be shortened ?10d)

- Prompt initiation of antibiotics clears the infection between 4 to 6 days
  - De-isolation at Day 7 of antibiotic treatment is a reasonable, safe and effective approach (vs 14d).
  - Follow up cultures D3/4 and Day5/6 vs Day 14? If follow up cultures positive review antibiotic dose, adherence, drug interactions & prolong course

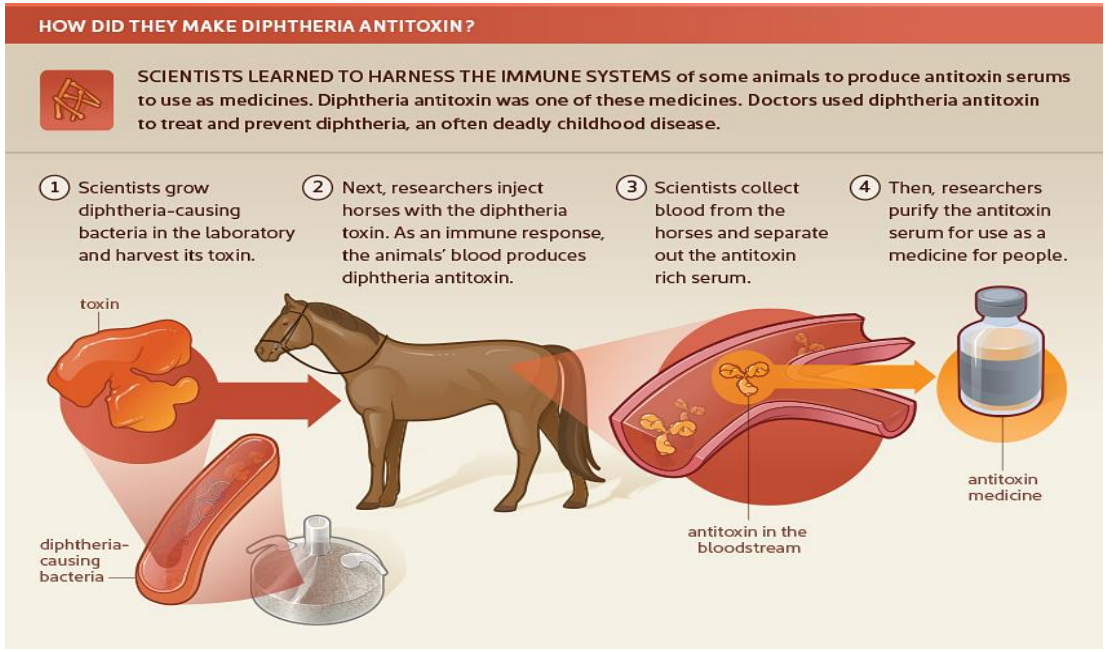
- *Alternatives = Penicillin or erythromycin, but need more frequent dosing, emerging penicillin resistance*
- *Resistance is being monitored by NICD*

- *Kills the organism and prevents further toxin production*
- *Slows the spread of local infection*
- *Reduces transmission*

Response to Antibiotics and DAT

Antitoxin (DAT)

- Horse Serum antitoxin: binds to and will inactivate diphtheria toxin
- **Do not delay!** Do not wait for lab results! Based on clinical suspicion – discuss with ID
- Once toxin internalized = too late!



***1894**. Roux et al. Paris*

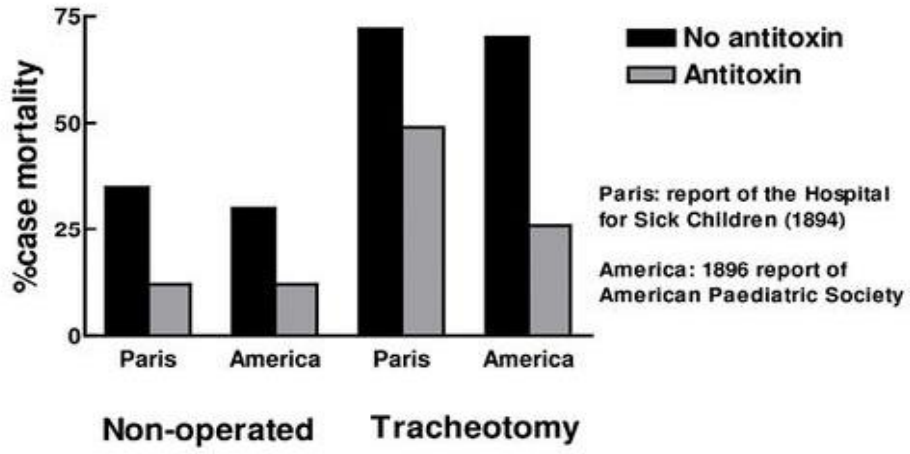


Table 9–1. **RELATIONSHIP BETWEEN MORTALITY FROM DIPHTHERIA AND DAY OF ILLNESS WHEN ANTITOXIN WAS FIRST GIVEN**

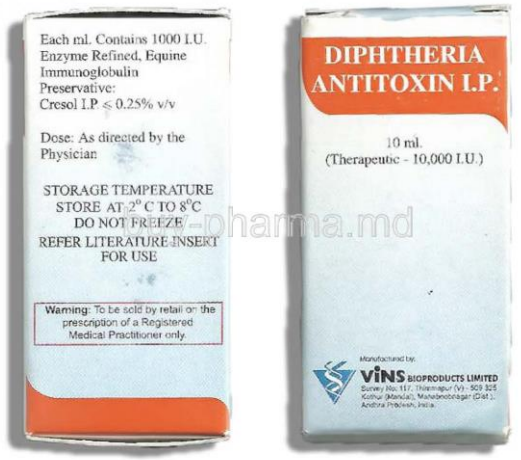
DAY OF ILLNESS ANTITOXIN GIVEN	UNITED KINGDOM		LOS ANGELES	
	Cases	Deaths (%)	Cases	Deaths (%)
1	329	1.5	235	4.2
2	2269	3.4	249	5.2
3	2407	6.9	273	9.2
4	1612	10.9	203	10.8
5	911	14.9	157	13.4
6	416	13.0	64	12.3
7	320	16.6	112	12.5
Later	327	15.3	104	20.2
Total	8591	8.3	1397	9.6

Adapted by permission of Oxford University Press from Ker CB. Infectious Diseases, A Practical Textbook (3rd ed). London, Oxford University Press, 1929, p 423; and Naiditch MJ, Bower AG. Diphtheria. A study of 1,433 cases observed during a ten-year period at Los Angeles County Hospital. Am J Med 17:229–245, 1954.

Picture: K. McArthy/ H.Rabie

Diphtheria Anti-Toxin (DAT)

Global DAT supply challenges!



- Consult hotline/ ID specialist prior to starting to confirm indication
- No need for sensitivity/ allergy testing
- **HCU/monitored setting:**
  - *SaO2, BP, Temp, Adrenalin 1:1000, salbutamol, IV antihistamine, corticosteroid – prednisone/hydrocortisone, IV fluid, O2 supply and devices on hand*
  - Premed optional (not recommended by WHO)
- Do not give repeat doses! Increase risk of hypersensitivity
- Section 21 – consent important
- Dosage depends on extent and duration of disease:

Severity of diphtheria	Dosage for adults and children	Number of vials required
• Laryngitis OR pharyngitis AND • Duration < 48 hours	20 000 IU	2
• Nasopharyngeal disease (extensive pseudo-membrane) AND • Duration < 48 hours	40 000 IU	4
One or more of: • Diffuse swelling of the neck • Any disease ≥ 48 hours • Severe disease (respiratory distress, shock)	80 000 IU	8

DAT: monitor for severe sensitivity reaction during and after DAT

Adverse event	Clinical description	Action
Anaphylaxis (rapid onset 0–20 minutes after the start of the infusion)	**Airway:** bronchospasm (hoarse voice, cough, wheeze), obstruction (stridor), dyspnoea, respiratory failure. **Cardiovascular:** hypotension, arrhythmias, rapid weak pulse, angioedema. Any decrease in conciousness level consider anaphylaxis.	Stop infusion immediately Call for help Administer epinephrine (adrenaline) 1:1000 by intramuscular (IM) injection. Dose = 0.01 mg/kg of body weight up to a maximum dose of 0.5 mg Repeat dose after 5 minutes for a maximum of TWO further doses if no improvement. Move the patient to a critical care area for continued management. Repeat vital signs every 5 minutes
Hypersensitivity reaction (within 20–60 minutes)	Skin: pruritus, flushing, urticaria (in absence of signs of anaphylaxis) Mild increase in temperature Mild tachypnoea	Stop the infusion, administer supportive treatment and inform the medical team. Repeat vital signs every 5 minutes, if symptoms remain mild, continue the infusion but slow the rate by 50%.
Serum sickness 7–10 days after initial exposure (range 5–25 days)	Fever Maculopapular rash, or urticaria in milder forms Arthritis, arthralgia and lymphadenopathy Rare: angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis or myocarditis	Mild cases of serum sickness frequently resolve spontaneously over a few days to 2 weeks. Antihistamines, non-steroidal anti-inflammatory drugs and corticosteroids may be helpful

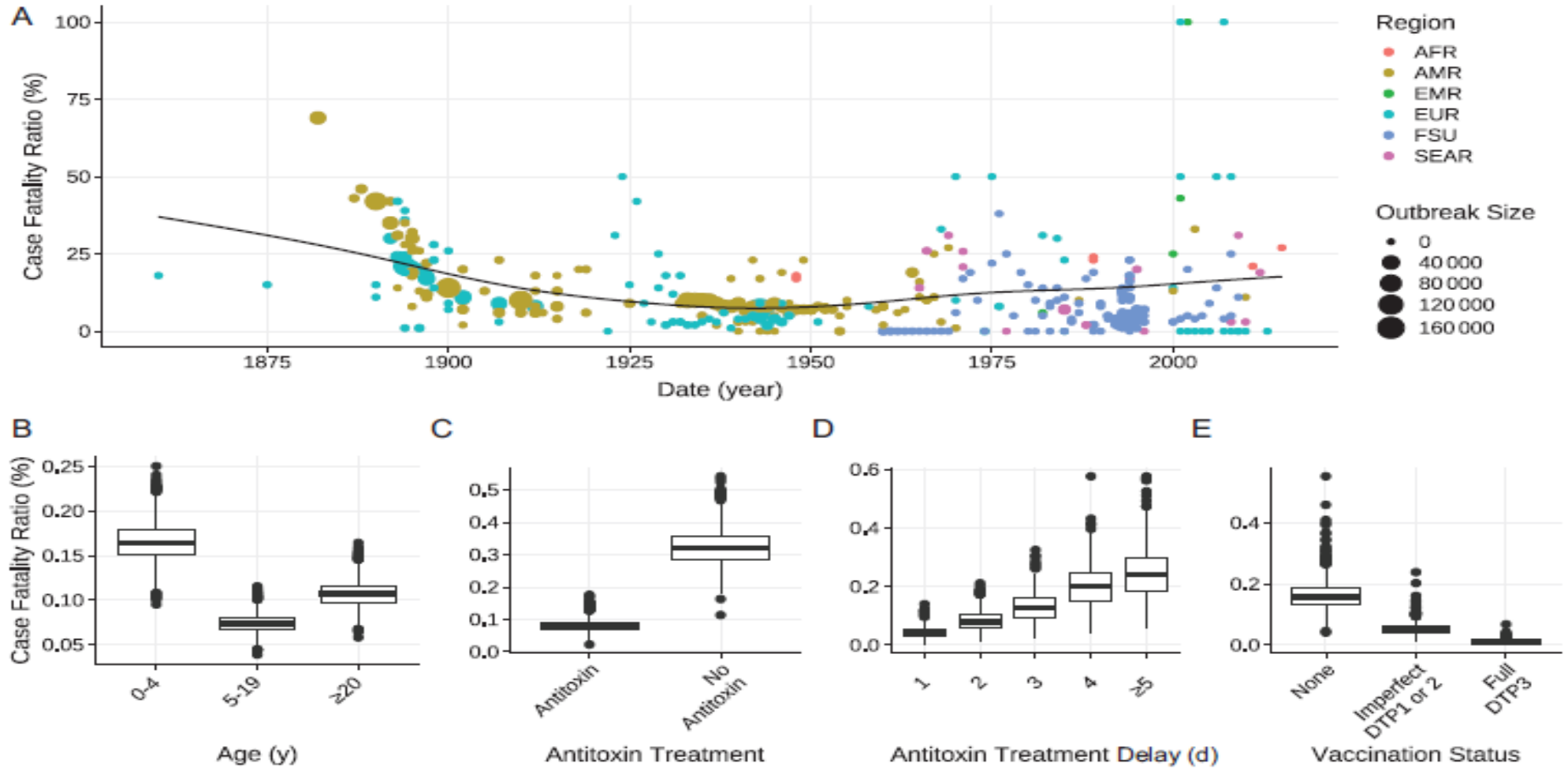
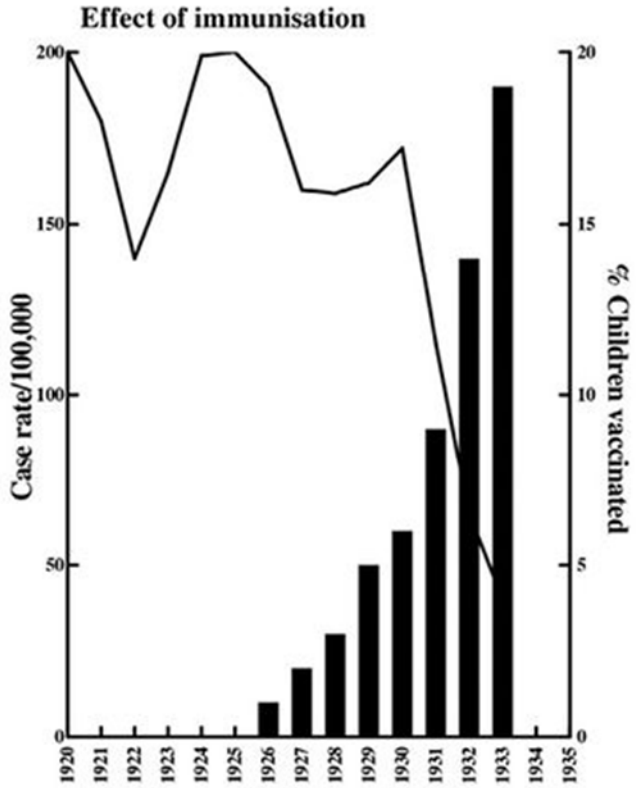


Figure 3. Case fatality ratio. *A*, Case fatality ratio by year, with World Health Organization (WHO) region (color), outbreak size (point size), and the weighted mean over time (black line). *B*, Case fatality ratio by age. *C*, Case fatality ratio by diphtheria antitoxin treatment. *D*, Case fatality ratio by diphtheria antitoxin treatment delay. *E*, Case fatality ratio by vaccination status. The former Soviet Union (FSU) is not a WHO region but is specific to the 1990–1998 outbreak. Abbreviations: AFR, African Region; AMR, Region of the Americas; DTP, diphtheria-tetanus-pertussis vaccine; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region.

Treatment – Supportive care & Vaccination

- **Supportive care**
  - airway protection,
  - ECG changes (every 24/48 hours)
  - Renal function (in/output, U&E)
  - Platelets and Hb
- **No DAT - Role of IV Ig ?Role of Mab?** Commercially available immunoglobulin preparations for intravenous use contain antibodies to diphtheria toxin - use for therapy of diphtheria is not proved or approved
- **Vaccinate** all cases in recovery phase – prior to discharge from hospital

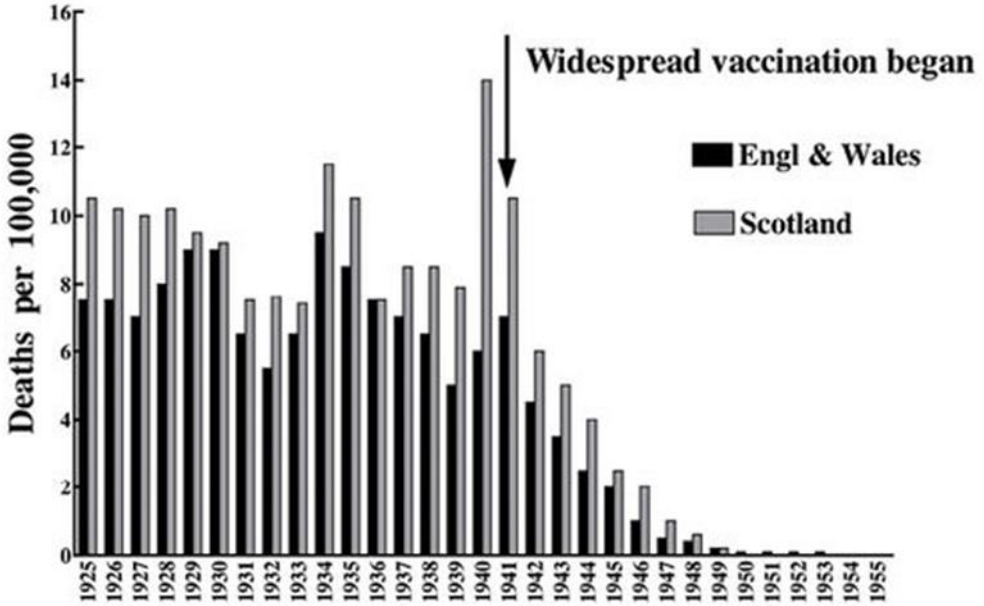


Public health response: contact tracing

- **Urgent response, category 1 notifiable condition**
- Notify and complete CIF in detail for patient (please give details of vaccine history)
- All household contacts
- Other contacts:
  - More than 15 minutes with 2 metres of patient (and no PPE)
- Take swabs Nasopharyngeal (wear PPE)
- **Post-exposure prophylaxis 7-day course Azithromycin (? 3 Days)**
- Vaccinate (encourage vaccination of children)
- Self-monitor for development of symptoms – may need DAT
- Isolate at home, avoid contact until swab result
- Positive Contact
  - Trace contacts
  - Reassess for symptoms
  - Consider 14 days of Azithromycin

Vaccination: staff (and adults)

- Recommended booster every 10y (CDC)
  - Not policy in public health system
- If staff exposed:
  - Risk assessment
    - Swab taking, intubation high risk
    - More than 15 min with 2 m of patient
  - Swab +Azithromycin if no PPE worn
  - Vaccinate
- Must still wear PPE even though vaccinated!



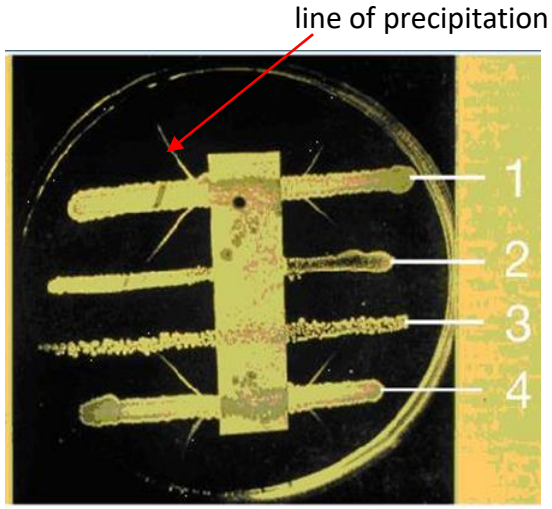
Laboratory confirmation of *Corynebacterium diphtheriae*

- Throat (oropharyngeal) swab should be collected, from below the pseudomembrane if possible.
- Placed in Amies transport medium (maintains viability)
  - If nothing else available, send a dry swab
    - To reach laboratory urgently
    - Culture yield may be decreased
- Submit to closest diagnostic laboratory for culture (MC&S [microscopy, culture, sensitivity]) and **diphtheria:**
  - MC&S will help to exclude other pathogens within the differential diagnosis, *e.g.* Group A streptococcus etc.
  - Consider respiratory viral screen: several ?diphtheria suspected cases were positive for respiratory viruses (SARS-CoV-2)
  - Possibility of co-infections
  - Do not wait for lab confirmation before initiating treatment

Laboratory methods (primary diagnostic)

- Culture using tellurite-containing medium (Hoyle's)
  - *C. diphtheriae* reduces potassium tellurite to tellurium to produce grey/black-coloured colonies
  - 72h incubation
- On blood agar, *C. diphtheriae* easily overlooked as glistening, creamy white colonies resembling *Staphylococcus* species
- All isolates and/or clinical specimens sent to the National Institute for Communicable Disease (NICD)
  - PCR confirmation of toxin (*tox*) gene
  - Phenotypic confirmation of toxin production (**Elek test**)
    - Also to exclude non-toxigenic toxin-gene bearing (NTTB)
    - No public health action needed for NTTB[1]
      - likelihood to revert to toxigenic is considered highly unlikely
- Submission of all isolates:
  - *C. diphtheriae*
  - *C. ulcerans* (zoonosis from companion animals - cats and dogs)
  - *C. pseudotuberculosis* (rare, zoonosis from sheep and goats)

C. diphtheriae on Hoyle's



Elek (toxin production)

[1] Public health control and management of diphtheria in England, 2024 guidelines; https://www.gov.uk/government/publications/diphtheria-public-health-control-and-management-in-england-and-wales, accessed Dec 2024.

NICD guidelines for diagnosis, testing, and treatment of diphtheria: https://www.nicd.ac.za/diseases-a-z-index/diphtheria/

GO VACCINATE!

Take home messages

- Have a high index of suspicion
- Act quickly for a suspected case
  - Ask for help if you are unsure
  - **NICD Hotline (0800 212 552)**
  - ENT/Infectious Disease specialist
  - Start treatment prior to lab confirmation
- **DAT saves lives**
  - **know where supply is and how to access it**
- Rapid public health response is essential to contain spread