

Revisited of Diphtheria : Treatment & Prevention

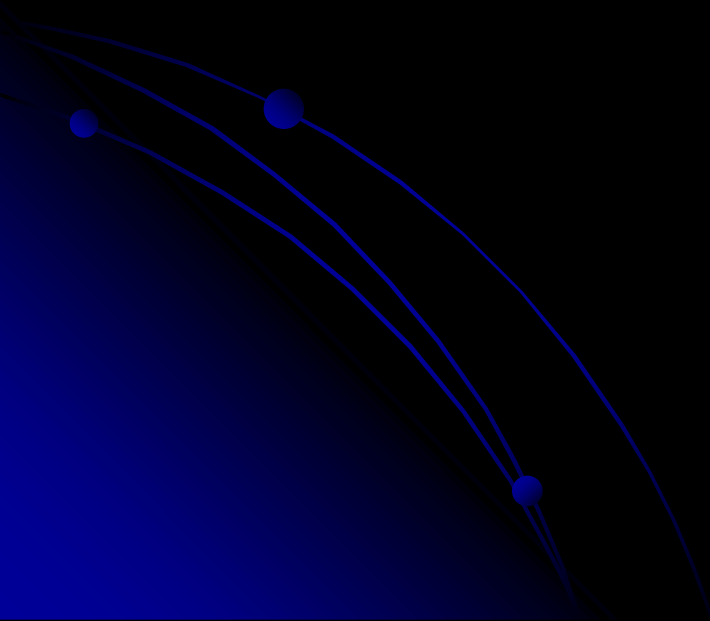
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**Queen Sirikit National Institute of Child Health,
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12 December 2013 , JITMM, Bangkok

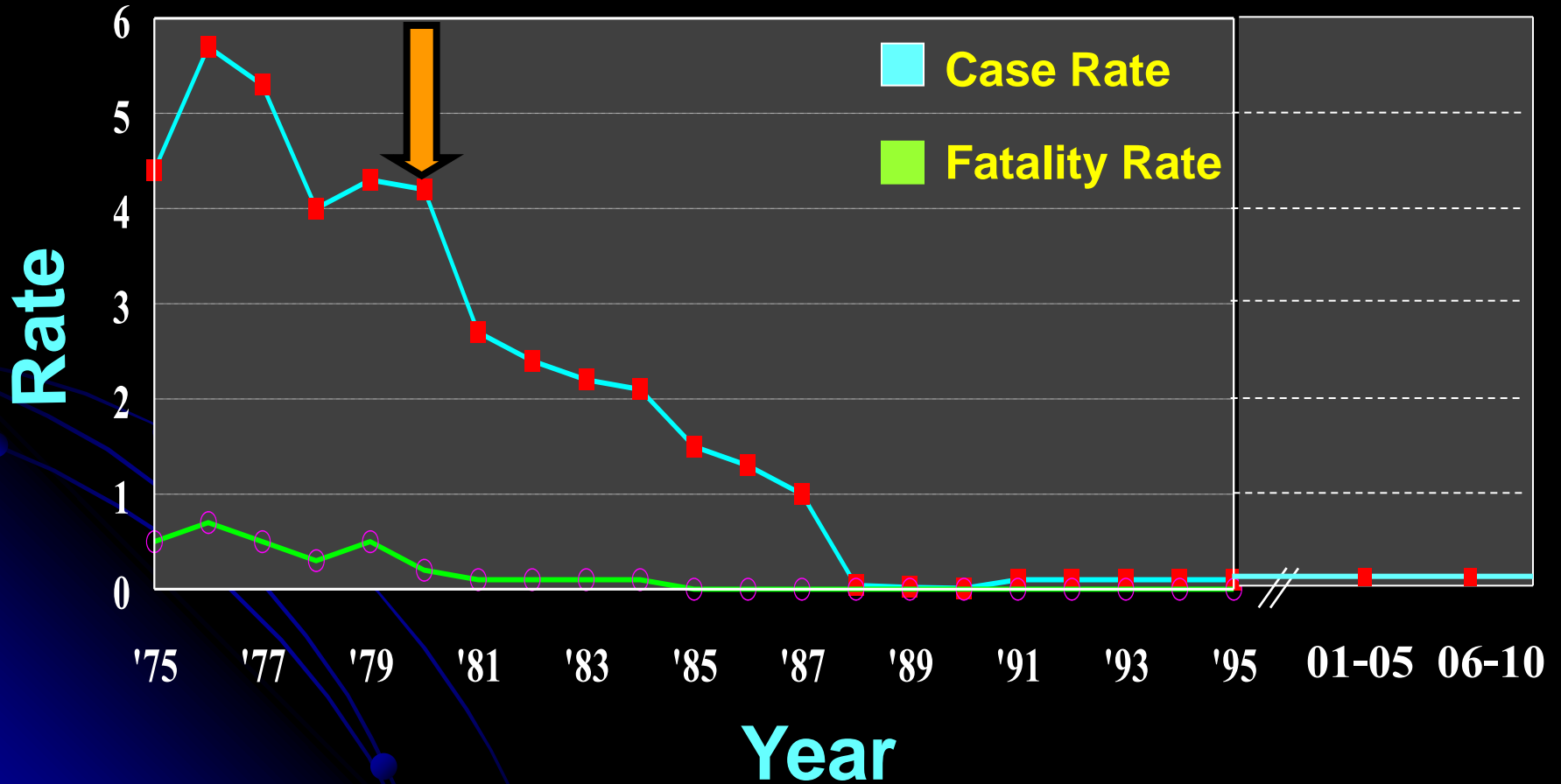
Diphtheria :-

**the forgotten disease in children and emerging
infectious disease in adult in Thailand?**



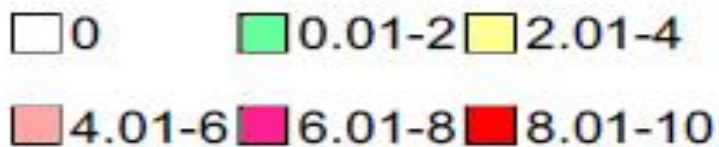
Diphtheria Situation in Thailand : 1975 - 1995 & 2001-2010

DPT vaccination
in EPI Program-1980

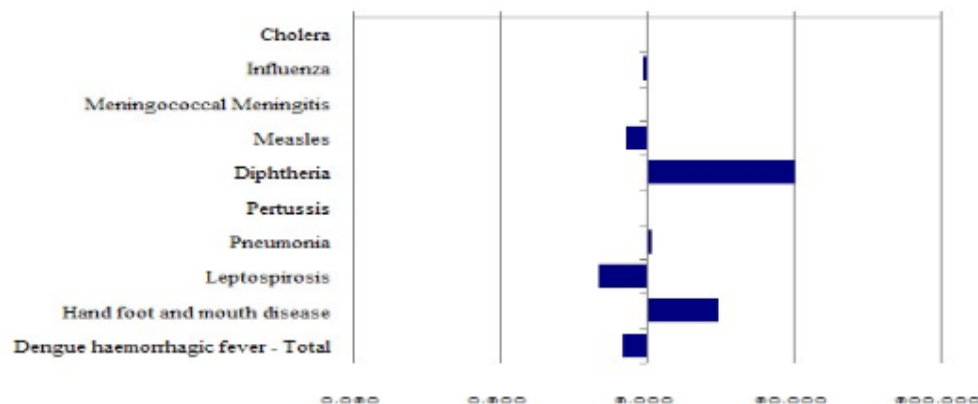




อัตราต่อแสนประชากร



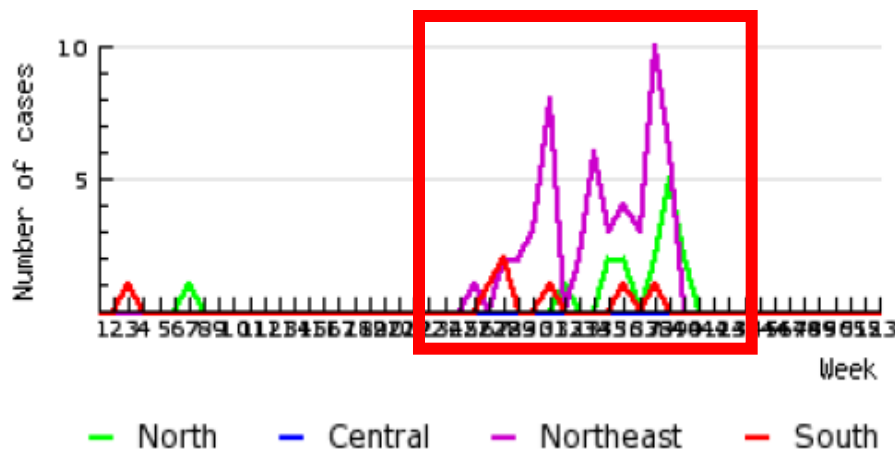
แผนภูมิ ๑ จำนวนผู้ป่วย ๔ สัปดาห์ปัจจุบันเปรียบเทียบกับจำนวนผู้ป่วยเฉลี่ย ๔ สัปดาห์ ๑๕ ช่วงของข้อมูล ๕ ปีย้อนหลัง (ข้อมูลถึงสัปดาห์ที่ ๓๙ วันที่ ๒๕ กันยายน - ๑ ตุลาคม ๒๕๕๕) ประจำวันที่ ๒ ตุลาคม ๒๕๕๕



- หมายเหตุ:
- ใช้มาตราส่วน Logarithm
 - จำนวนผู้ป่วยเฉลี่ย ในช่วง 4 สัปดาห์ 15 ช่วง ได้แก่จำนวนผู้ป่วยในช่วง 4 สัปดาห์ก่อนหน้า 4 สัปดาห์เดียวกับปัจจุบัน และ 4 สัปดาห์ หลัง ของข้อมูล 5 ปี ย้อนหลัง
 - ถ้าปรากฏแถบสีเหลืองจากแท่งที่ปรากฏ ไปทางขวาแสดงว่าจำนวนผู้ป่วยในช่วงปัจจุบัน $> x + 2SD$
 - ถ้าปรากฏแถบสีเหลืองจากแท่งที่ปรากฏ ไปทางซ้ายแสดงว่าจำนวนผู้ป่วยในช่วงปัจจุบัน $< x - 2SD$

Number of Diphtheria cases by week of onset and region.

2555

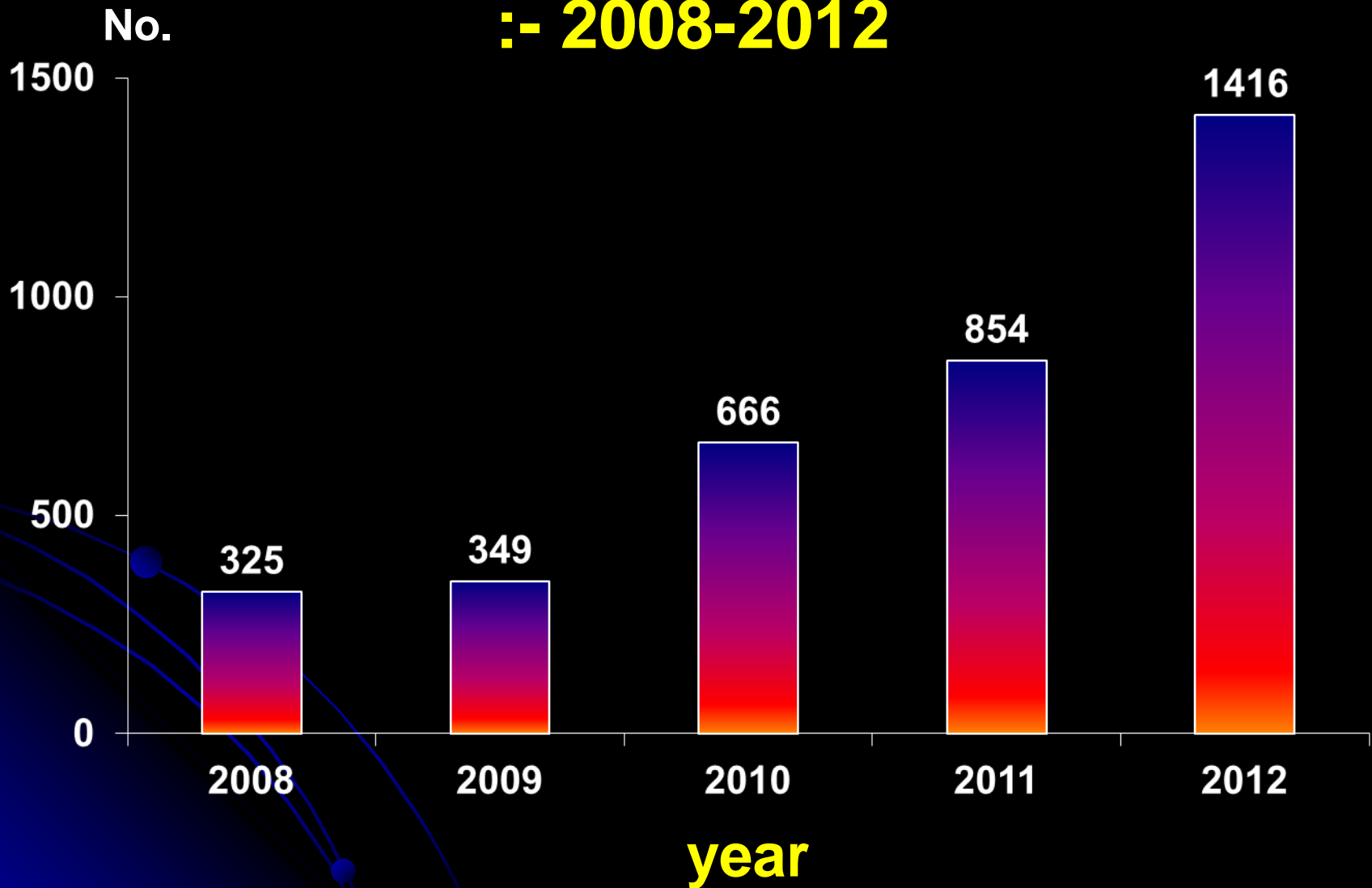


Diphtheria Incidence in ASEAN Countries - WHO 2012

Country	2012	2011	2010	2009	2008
Brunei	0	0	0	0	0
Cambodia	-	-	3	3	7
Indonesia	1192	806	432	189	219
Lao PDR	130	0	34	0	2
Malaysia	0	0	3	0	4
Myanmar	19	7	4	19	3
Philippines	-	-	107	118	65
Singapore	0	0	0	0	0
Thailand	63	28	77	12	8
Vietnam	12	13	6	8	17

Diphtheria Cases among ASEAN Countries

:- 2008-2012



(WHO incidence of Diphtheria 2012.)

What're the different of 2012 diphtheria epidemic from previous years in Thailand?

- Epidemic occurring in different areas
 - New strain of *C.diphtheriae* from previous year
 - Age of patients shift to adult age (~50% adult)
 - Although number of case were quite similar to previous year
-

Pathogenesis



Pathogenesis and pathology of Diphtheria (1)

- *C. diphtheriae* grow in respiratory tract and skin
- Pathogenesis of disease caused by exotoxin (62-kd polypeptide)

- Exotoxin -----> causes epithelial cell death, fibrin, WBC, RBC etc.

↓
Pseudomembrane greyish or brownish
difficulty in removal of patch, bleeding

(Nelson Textbook of Pediatric, 17th edition, P886-889.)

Pathogenesis and pathology of Diphtheria (2)

- Exotoxin ---> Cardiomyopathy ---> myocarditis (1-2 wk)
 - > Demyelination of nerve ---> neuritis (2-8 wks)
 - > Necrosis of renal tubule ---> nephritis (2-10 wks)
 - > Blood components ---> thrombocytopenia (2-10 wks)
 - Hospital observation for complications around 2-4 weeks
-

(Nelson Textbook of Pediatric, 17th edition, P886-889.)



Diagnosis of Diphtheria

Ways of diagnosis of Diphtheria

1. Epidemiological diagnosis

2. Clinical diagnosis

3. Laboratory diagnosis



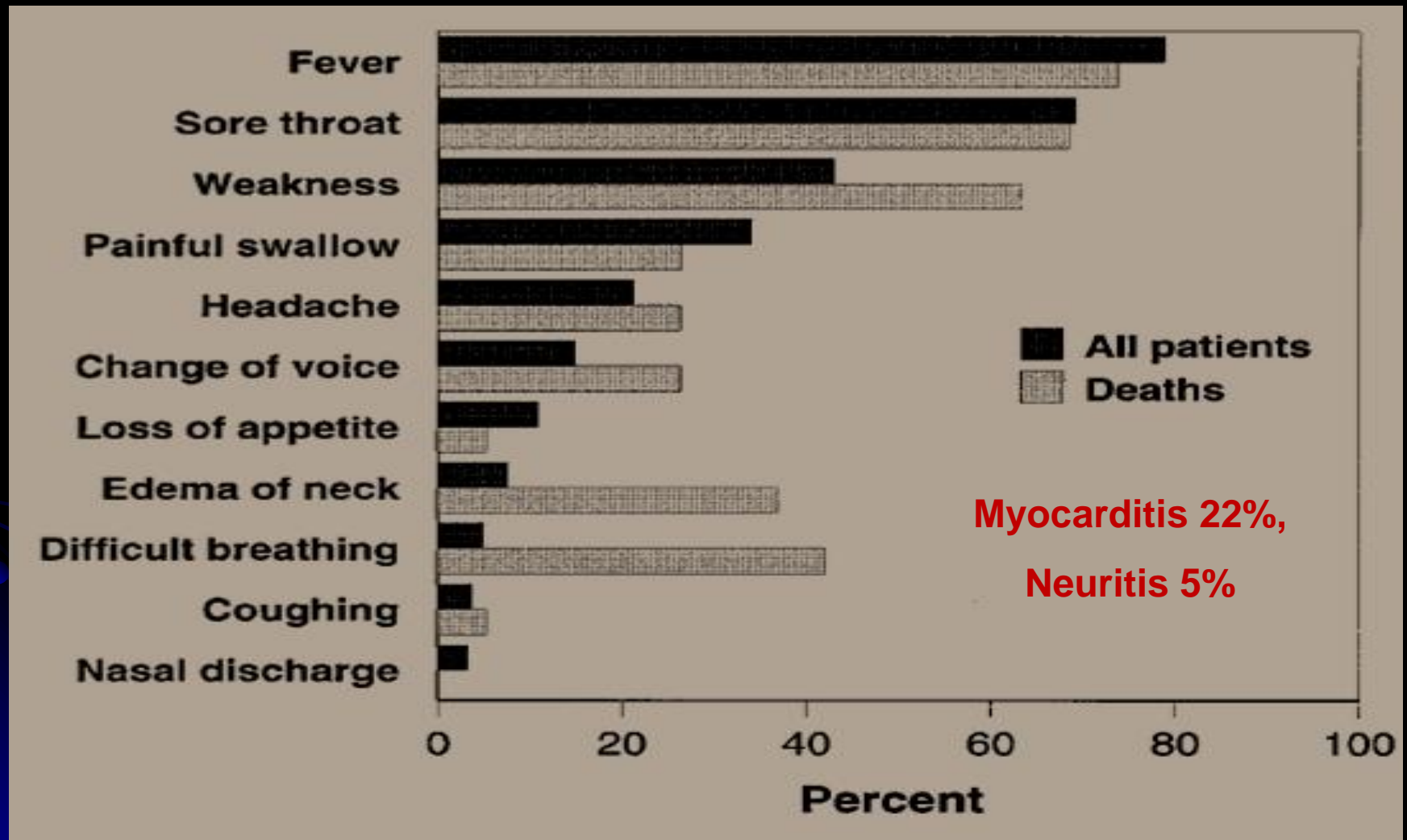


Clinical Manifestation

Clinical Manifestation of Diphtheria

- Non-toxin-producing strain of *C.diphtheriae* will not causes diphtheria, may causes mild pharyngitis
 - Clinical manifestation caused by toxin (patch, toxemia)
 - Incubation period 1-5 days
 - **Low grade fever**, membrane develops 2-3 days. after onset, lymphadenopathy, systemic toxicity
 - **Complication**:- myocarditis(1-2wk), neuritis(2-8 wks)
-

Frequency of presenting symptoms among all hospitalized diphtheria patients and 19 diphtheria deaths, Kyrgyz Republic, 1995



(Kadirova R. JID 2000; 181(Suppl 1):S110-5.)

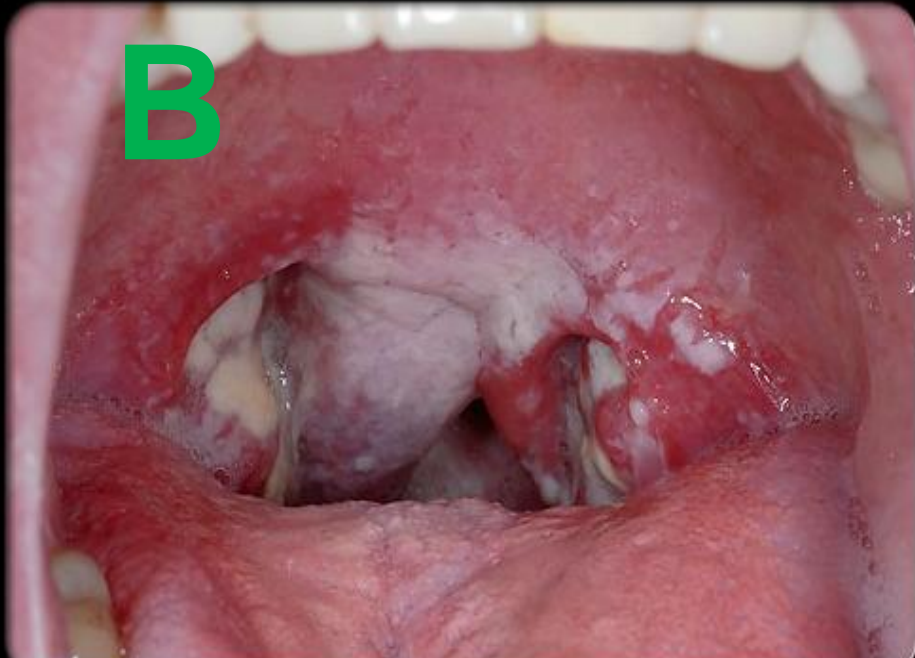
“Throat Patch” Differential Diagnosis

- 1. Diphtheria**
 - 2. Streptococcal pharyngotonsillitis and other streptococcal pharyngitis**
 - 3. Infectious mononucleosis**
 - 4. Moniliasis**
 - 5. Post Tonsillectomy**
 - 5. Adenoviral infection**
 - 6. Agranulocytosis**
 - 7. Histiocytosis X (Letterer-Siwe Syndrome)**
-

A



B



C



D



A



**August 2012, A Cambodian boy aged 14 yr. High fever for 2 d.
very painful throat, no dyspnea or tachypnea
:- Throat culture:- numerous *Streptococcus viridans***

B



Acute pharyngotonsillitis from Streptococcus gr. A.

C



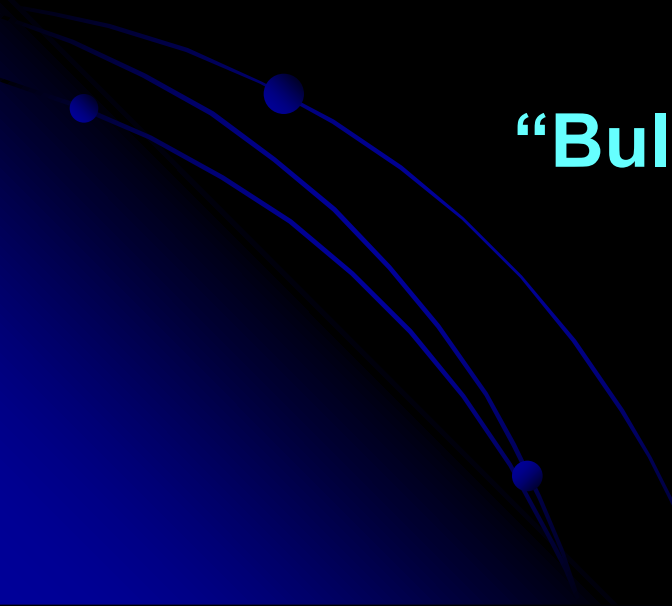
Exudative Tonsillitis from *C.diphtheriae*

D



**Exudative Tonsillitis from EBV
(Infectious mononucleosis)**

**Toxemia, swelling
of neck, lymph node
enlargement with fatal
outcome in
“Bullneck diphtheria”**





Cutaneous diphtheria

“Croup Syndrome” Differential Diagnosis

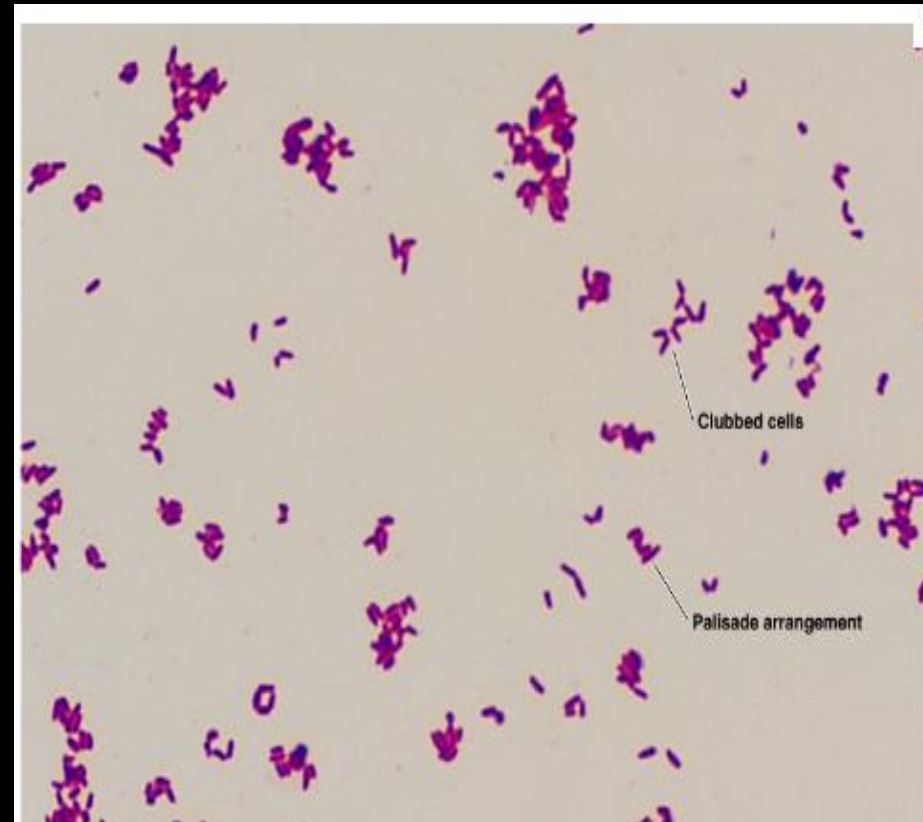
Croup = Upper airway obstruction from any causes

1. **Viral croup eg. PIV, influenza, RSV, etc.**
 2. **Bacterial croup eg. Diphtheria, Staphylococcal tracheitis etc.**
 3. **Foreign body in upper or lower respiratory tract**
 4. **Epiglottitis eg. viral or bacteria (Hib)**
 5. **Spasmodic croup**
-

Laboratory Findings



Gram stain of Diphtheria patient :- gram positive bacilli, club shaped, Chinese character



Laboratory diagnosis of C. diphtheriae

- Throat Swab from patch , Gram stain found “Chinese letter”
(practically not easy to find)
- Throat Swab from patch , under patch for culture in sheep
blood and Tellurite media -Amie

↓
Blood agar plate

↓
Corynebacterium (day 3)

gram stain
(+ve bacilli)

Biochem.

Gel diffusion

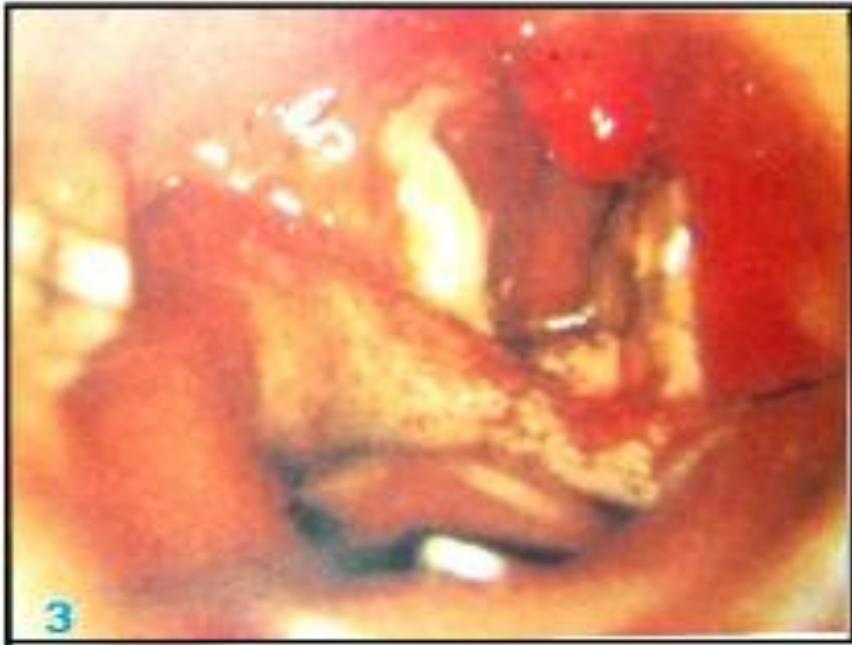
test toxin (day 5-6)



Clinical Management of Diphtheria

Decision in treating Diphtheria

1. Find throat patch , then consider Rx diphtheria
 2. Throat patch + sign of upper airway obstruction
; Rx diphtheria immediately
 3. Throat patch only
 - see color of patch , try to remove with difficulty ?
 - gram stain , culture for *C.diphtheriae* from patch
 - WBC
-



Treatment of Diphtheria in Suspected/Confirmed Case

1. IV DAT immediately after skin test

2. Throat swab/patch gram stain, culture with toxin test

3. Antibiotic - Penicillin, Erythromycin

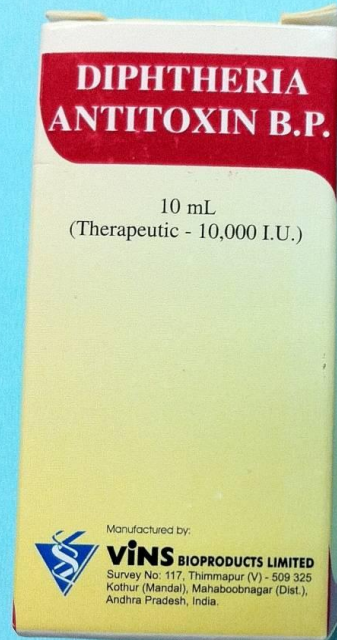
4. Symptomatic and Supportive cares ,

observe for complications eg. myocarditis, neuritis etc.

Diphtheria Antitoxin : DAT



Diphtheria Antitoxin [14]



Dosage of DAT in Suspected/Confirmed Diphtheria

- **mix DAT in Normal saline, IV drip (slowly in hours)**

- Anterior nasal 10,000 - 20,000 units
- Pharyngeal or laryngeal (ภายใน 2 วัน) 20,000 - 40,000 units
- Nasopharyngeal or combine type 40,000 - 60,000 units
- Bull neck or onset more than 3 days 80,000 -120,000 units

- **No need to repeat DAT ,may increase side effects**

Skin Test for Diphtheria Antitoxin (DAT)

- In general human will have hypersensitivity to horse serum 5-20%
- Horse serum skin test process
 - :- inject dilute 1: 1000 dose 0.02 c.c. ID
 - :- if possible
 - positive control with Histamine
 - negative control with saline
 - :- observe 15-20 min.
 - :- reaction size 3 m.m. or more than negative control = positive
 - :- DAT need desensitization - if skin test positive

Desensitization of Horse Serum, IV

- IV is recommended
- inject IV every 15 min. then closely observe ;
 - 0.1 ml of 1:1000 dilution. IV
 - 0.3 ml of 1:1000 dilution. IV
 - 0.6 ml of 1:1000 dilution. IV
 - 0.1 ml of 1:100 dilution. IV
 - 0.3 ml of 1:100 dilution. IV
 - 0.6 ml of 1:100 dilution. IV
 - 0.1 ml of 1:10 dilution. IV
 - 0.3 ml of 1:10 dilution. IV
 - 0.6 ml of 1:10 dilution. IV
 - 0.1 ml of undilute dilution. IV
 - 0.3 ml of undilute dilution. IV
 - 0.6 ml of undilute dilution. IV
 - 1 ml of undilute dilution. IV the rest of DAT give IV slowly

Treatment of Diphtheria in Suspected/Confirmed Case

1. IV DAT immediately after skin test

2. Throat swab/patch gram stain, culture with toxin test

3. Antibiotic - Penicillin, Erythromycin

4. Symptomatic and Supportive cares ,

observe for complications eg. myocarditis, neuritis etc.

Dosage of Antibiotics in Suspected/Confirmed Case

Children :- PGS 100,000 – 200,000 unit/kg/d, q 6 hr.x 14 days

:- Erythromycin 50 mg/kg/d, q 6 hr.x 14 days

Adult :- PGS 3-4 Million unit, IV drip, q 6 hr. x 14 days

:- Erythromycin 2 gm/d, q 6 hr.x 14 days



Treatment of Diphtheria in Suspected/Confirmed Case

1. IV DAT immediately after skin test
 2. Throat swab/patch gram stain, culture with toxin test
 3. Antibiotic - Penicillin, Erythromycin
 4. Symptomatic and Supportive cares , observe for complications eg. myocarditis, neuritis etc.
-

Observation of Complications from Diphtheria

1. Admit in isolated room, absolute bed rest 2-4 weeks

2. Daily observe

2.1 record vital sign q 6 hr.

2.2 record intake / output daily

2.3 observe “ nasal voice ”

2.4 observe for aspiration when eating , drinking

3. Lab. Investigation

3.1 EKG daily

3.2 urine exam q 1-2 day/time

3.3 repeat throat culture when complete 14 d. of antibiotic

Diphtherial Myocarditis

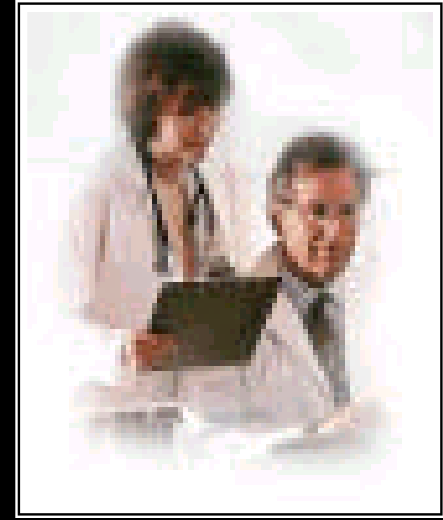
- Occur on 1-6 wks. after onset (commonly at week 2-3)
 - Incidence 10-25% of case; death 50-60%
 - Most important factor is DAT timely and appropriate dose
 - Treatment of heart failure; dopamine, dobutamine, milrinone
 - Steroid, IVIG are NO BENEFIT
 - Symptoms :- sinus tachycardia
 - :- prolonged PR interval, ST-T wave change
 - :- 1st, 2nd, 3rd – degree heart block
-

Diphtherial Neuritis

- Occur on 2-3 wks. after onset , facial N. paralysis on week 5
 - Symptom :-numbness
 - :- paralysis of soft palate
 - :- paralysis of post pharyngeal, laryngeal, facial N
 - :- observe “ nasal voice ”
 - :- symmetric polyneuropathy eg. motor weakness, reflex ↓ , strabismus, blurred vision
 - :- GBS- like syndrome
-

Pitfall in Management of Diphtheria

1. Avoid put endotracheal tube , should tracheostomy if airway obstruction (can cause bleeding and induce absorption of toxin from patch)
 2. Oxygen mask usually no benefit
 3. Steroid usually no benefit
 4. If suspected diphtheria give DAT , antibiotic immediately and throat swab culture for *C.diphtheriae* until 2 negative culture.
-



Prevention of Diphtheria

DAT Level for Protection

- DAT <0.01 IU/ml = no protection
- DAT 0.01-0.1 IU/ml = partial protection
- DAT \geq 0.1 IU/ml = full protection
- DAT \geq 1.0 IU/ml = long term protection
(several years)

(N Engl J Med 1954; 251: 459-66.)

How many doses of Td for good protection?

During diphtheria outbreak

How many dose of diphtheria toxoid (Td.) is enough?

1 or 2 or 3 ???



Immunogenicity of Tetanus-Diphtheria Toxoids (Td) among Ukrainian Adults: Implications for Diphtheria Control

Table 2. Seroprevalence (by subject age group) of protective diphtheria antitoxin titers (≥ 0.1 IU/mL) during study period—Kiev, 1994–1995.

Age group, years	Diphtheria antitoxin ≥ 0.1 IU/mL				
	Day 0 (<i>n</i> = 488)	Day 7 (<i>n</i> = 488)	Day 30 (<i>n</i> = 477)	Day 60 (<i>n</i> = 472)	Day 425 (<i>n</i> = 385)
18–29	84.9	94.3	99.0	99.0	89.4
30–39	35.3	72.5	92.9	97.1	77.2
40–49	18.4	46.1	70.5	78.4	57.5
50–67	44.5	87.9	97.9	98.0	92.9
Total	43.0	72.7	88.7	92.2	76.6

NOTE. Data are % of subjects.

Immune Response to Diphtheria Booster Vaccine in the Baltic States

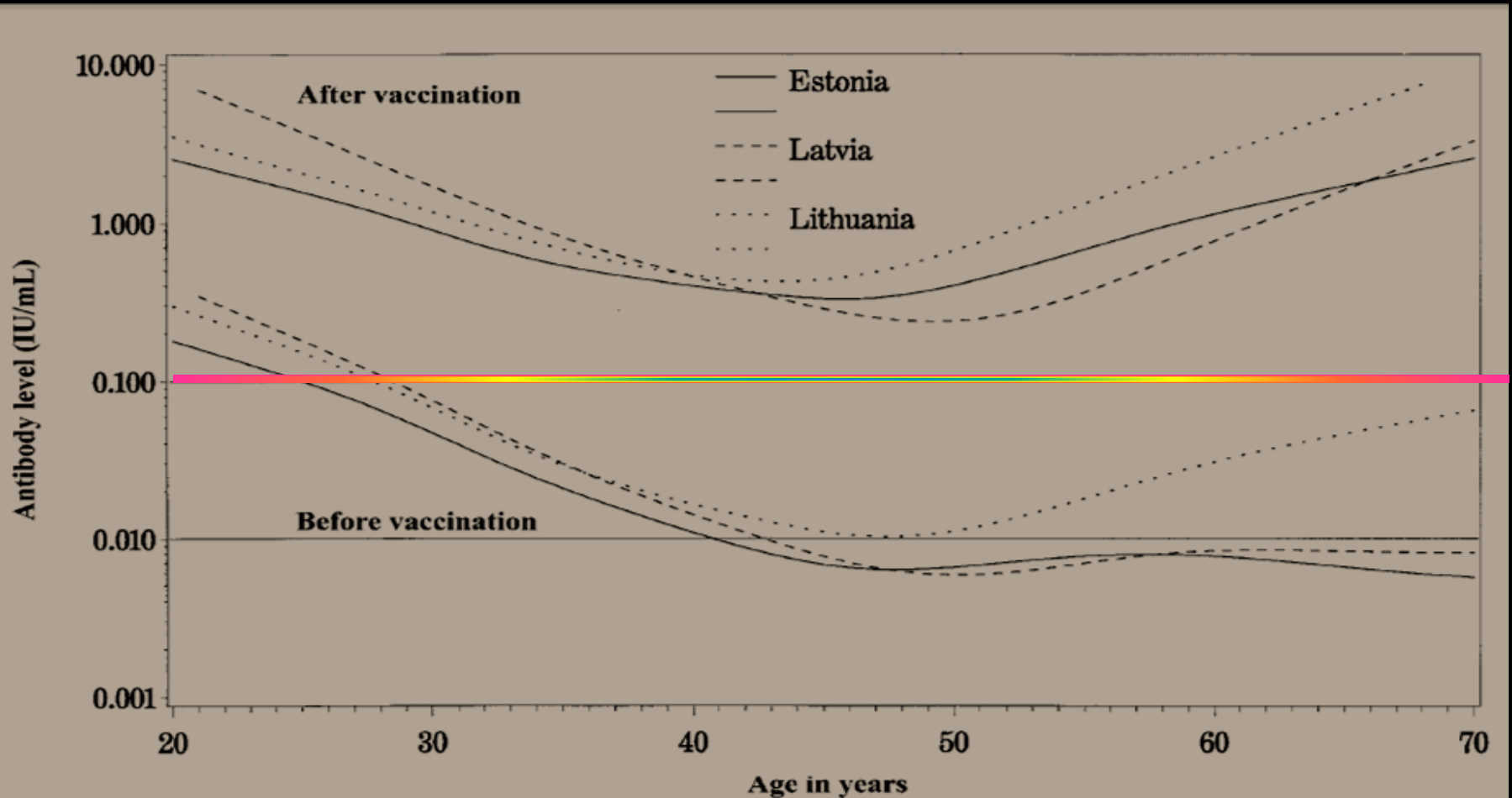


Figure 2. Smoothed age-specific median diphtheria antibody levels in study participants before and after vaccination, according to country

(Ronne T., JID2000;181(Suppl1):S213-9.)

Vaccine DPT, Td in Thailand

- **DPT in EPI program started on 1977 (2 doses)
(provided 3 doses on 1985)**
 - **Td for booster in pupils on 1982**
 - **Td for booster in pregnancy on 2005**
-

Adverse Reaction of Td vaccine

- **Local reactions eg. redness, pain, swelling etc. are common**
 - **Severe swelling, redness, pain (Arthus-like reaction) can be found at 2-8 hr after Td vaccination , usually found in individual whom had very high anti- Tetanus and/or anti-Diphtheria antibodies. If it occurred, that patient should not vaccinated Td for at least 10 years.**
-



A nurse age 30 year old had received one dose of Td , 4 hours later , the injection site had 12 cm. of swelling, redness, mild pain. This picture was taken 2 days after vaccination.

Composition of Td, Tdap (Adacel[®] and Boostrix[®])

Component	Td	Adacel [®]	Boostrix [®]
• Tetanus toxoid	7.5 Lf	5 Lf	5 Lf
• Diphtheria toxoid	2 Lf	2 Lf	2.5 Lf
• Pertussis components			
- PT	-	2.5 µg	8 µg
- FHA	-	5 µg	8 µg
- Pertactin (PRN)	-	3 µg	2.5 µg
- Fimbrial agglutininogen 2, 3	-	5 µg	-

Td / Tdap Vaccination, 2011- 2012 (USA)

- Tdap can be used as booster dose in 4-6 yr.(Thailand) or 10-12 yr.
- Tdap 1 dose to replace Td every 10 years
- **Adult 19 - < 65 yr. (never had received Tdap)(before 2011)**
 - Pregnancy > 20 weeks gestation, including father
 - Household members of infant <12 month of age
 - Health care provider
- Adult > 65 yr. whom had close contact children age <12 m.
- Adult whom had known or unknown history of Td 3 doses should have Tdap one dose in three of the series .

Hospital Infection Control of *C. diphtheriae*

1. Respiratory diphtheria

- with droplet precaution**
- by using mask, glove, gown, (goggle)**

2. Cutaneous diphtheria

- with contact precaution**
- by using glove, gown**

3. Admit in single room or cohort ward

Acknowledgement

- 1. Dr Sukuman Huntontan** **Dansai Hospital** **Loi Province**
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-