HPVC

ศูนย์เฝ้าระวังความปลอดภัยด้านผลิตภัณฑ์สุขภาพ

Health Product Vigilance Center

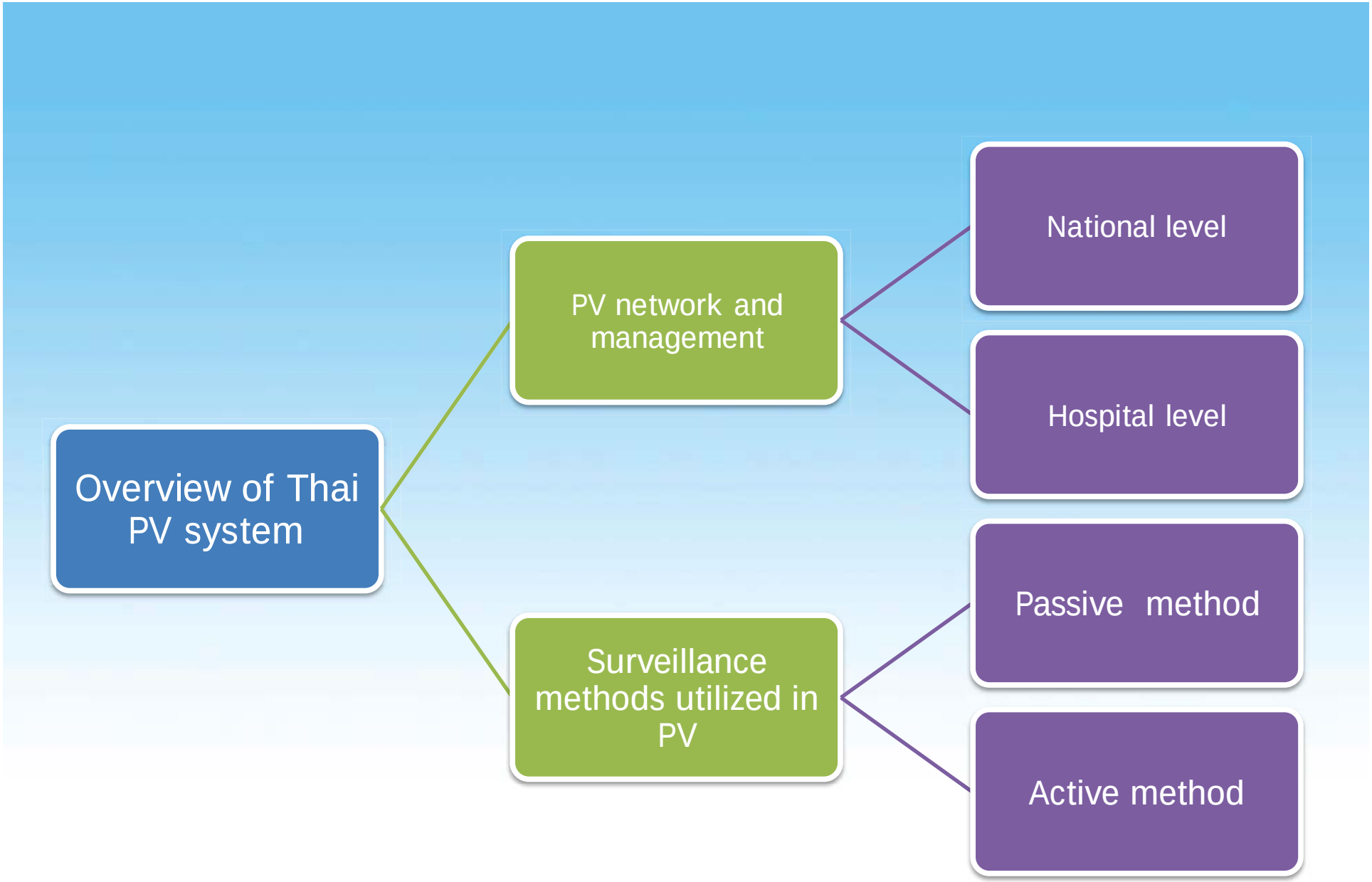
สำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข

Pharmacovigilance in Thailand

Ms. Wimon Suwankesawong
Head of Health Product Vigilance Center
Food and Drug Administration
Thailand

Outline

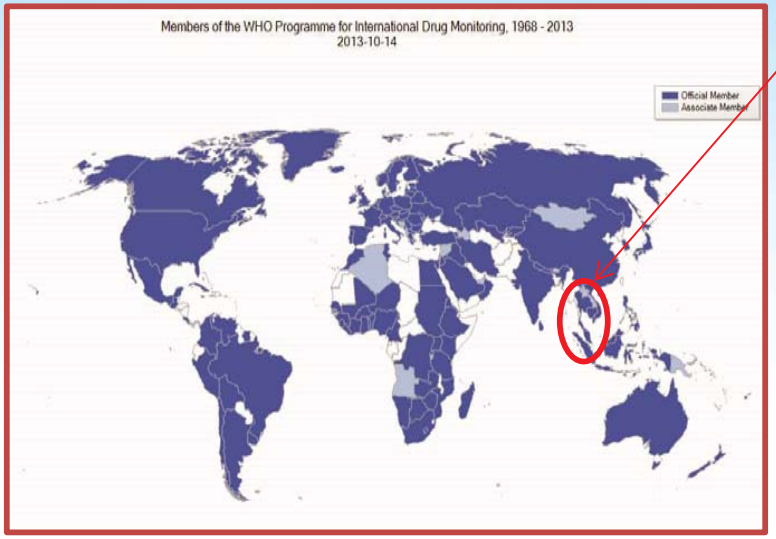
- Overview of Thai PV system
- Thai Vigibase
- PV & PGx Research


Overview of Thai PV system
PV network and management
National level
Hospital level
Surveillance methods utilized in PV
Passive method
Active method

Thailand

- Population : 64.8 million (2014)
- Provinces : 77

- PV system and National Center were set up in 1983.
- Thailand joined WHOPIDM as 26th member in 1984



HPVC

Thai PV network and management : National level

Sources of reports

Drug stores/clinic

Hospitals

(1,000-1,500)

Research partnerships

Academia

DMSC

Voluntary

MAH

Regulatory requirement

Safety Monitoring Program

HPVC

Thai Vigibase

Signal detection

Safety Signal WG &
PV Advisory subcommittee

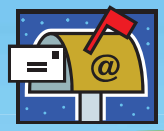
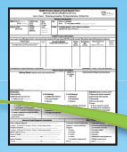
Regulation

Communication

Drug committee

Regulatory Action

Flow of reports and feedback loop in Thailand

AE online reporting system

Sources of reports

Hospitals

Rx: Drug stores

MAH

www.fda.moph.go.th/vigilance

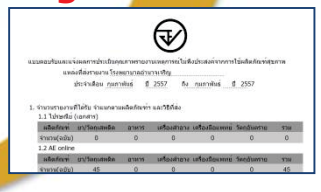
Thai FDA : HPVC

Alert

Annual Report

BULLETIN

Acknowledgement



HPVC

Safety Monitoring Program

- Status of conditional approval new drug
  - specially controlled drug = prescription drug
- Distribution
  - only to medical institutes and hospitals
- Drug safety monitoring
  - ADR reports (ICSRs)
- Report: every 4 months
  - volume of production, re-packing or importation
  - sale volume
  - Summary of drug safety monitoring

HPVC

Pharmacovigilance at Hospital Level

Submit reports to NHPVC

Follow up

Patients

Minimize Risk

- Counselling
- Provide alert cards

ADR Diagnosis

ADR Treatment

Pharmacists

1 PV contact person

Notify Rx

Physicians

Data collecting, Causality assessment & feed back to reporter

Drug Alert Cards

บัตรแพ้ยา/เตือนเรื่องยา

โปรดแสดงบัตรนี้ทุกครั้งเมื่อรับการตรวจรักษาหรือรับยา

เพื่อตรวจสอบว่าท่านได้รับยาที่อาจเกิดอาการแพ้ตามที่ระบุไว้หรือไม่

ชื่อ-สกุล.....HN. .....

ที่อยู่.....

โรงพยาบาล/สถานพยาบาล .....

แพ้ยาอาจถึงตาย หากมีอาการผิดปกติหรือสงสัยว่าแพ้ยาตัวใด ให้หยุดยานั้นทันที และนำตัวอย่างยาดังกล่าวพร้อมซองยา (ถ้ามี) ไปปรึกษาแพทย์หรือเภสัชกร

ข้อควรปฏิบัติ

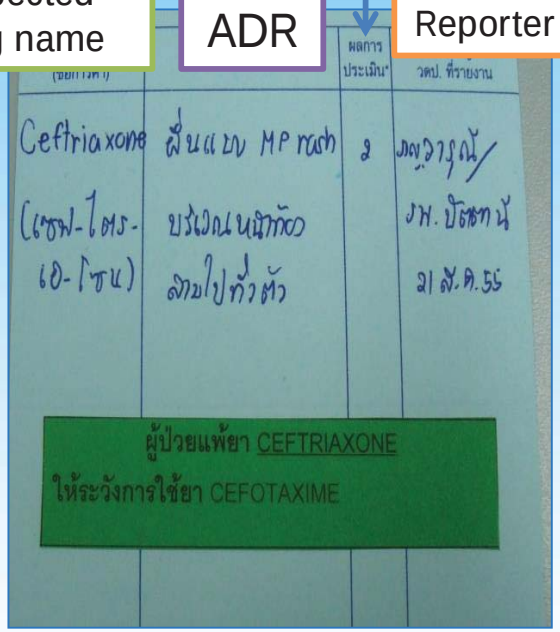
1. จดจำชื่อยาที่ท่านเคยแพ้
2. บอกแพทย์ผู้รักษา หรือผู้จ่ายยา หรือยื่นแสดงบัตรนี้ทุกครั้งที่ซื้อยา
3. หลีกเลี่ยงยา กลุ่มยา ที่เคยแพ้หรือเกิดอาการไม่พึงประสงค์
4. หลีกเลี่ยงการใช้ยาที่ไม่ทราบชื่อ ยาชุด ยาชง
5. สอบถามชื่อยา สรรพคุณ วิธีใช้ อย่างละเอียด เมื่อต้องใช้ยาใดๆ ก็ตาม
6. ยาในบัตรนี้สามารถใช้ได้ หากแพทย์เห็นว่าผู้ป่วยจำเป็นต้องได้รับยาชนิดนั้น หรือกลุ่มนั้น หรือยอมให้เกิดอาการไม่พึงประสงค์ เพื่อรักษาอาการของโรคที่รุนแรงและอันตรายกว่า หรือกรุณาสอบถามเหตุผลจากแพทย์

Causality assessment

Suspected drug name

ADR

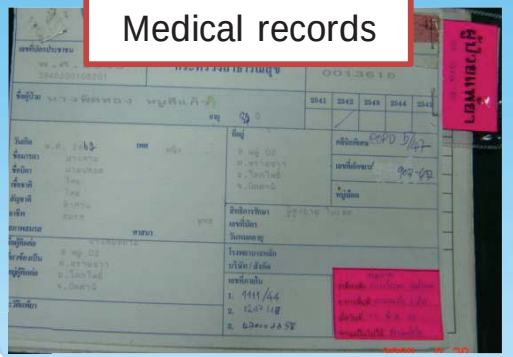
Reporter



SCARs cards

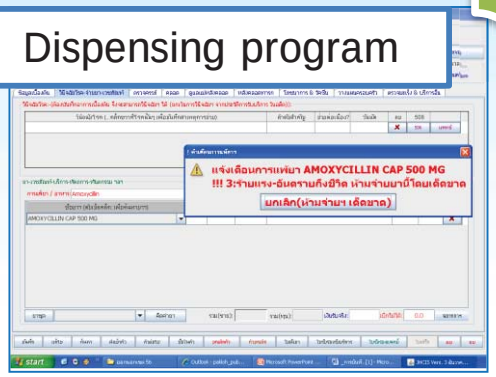
Patient chart

Medical records

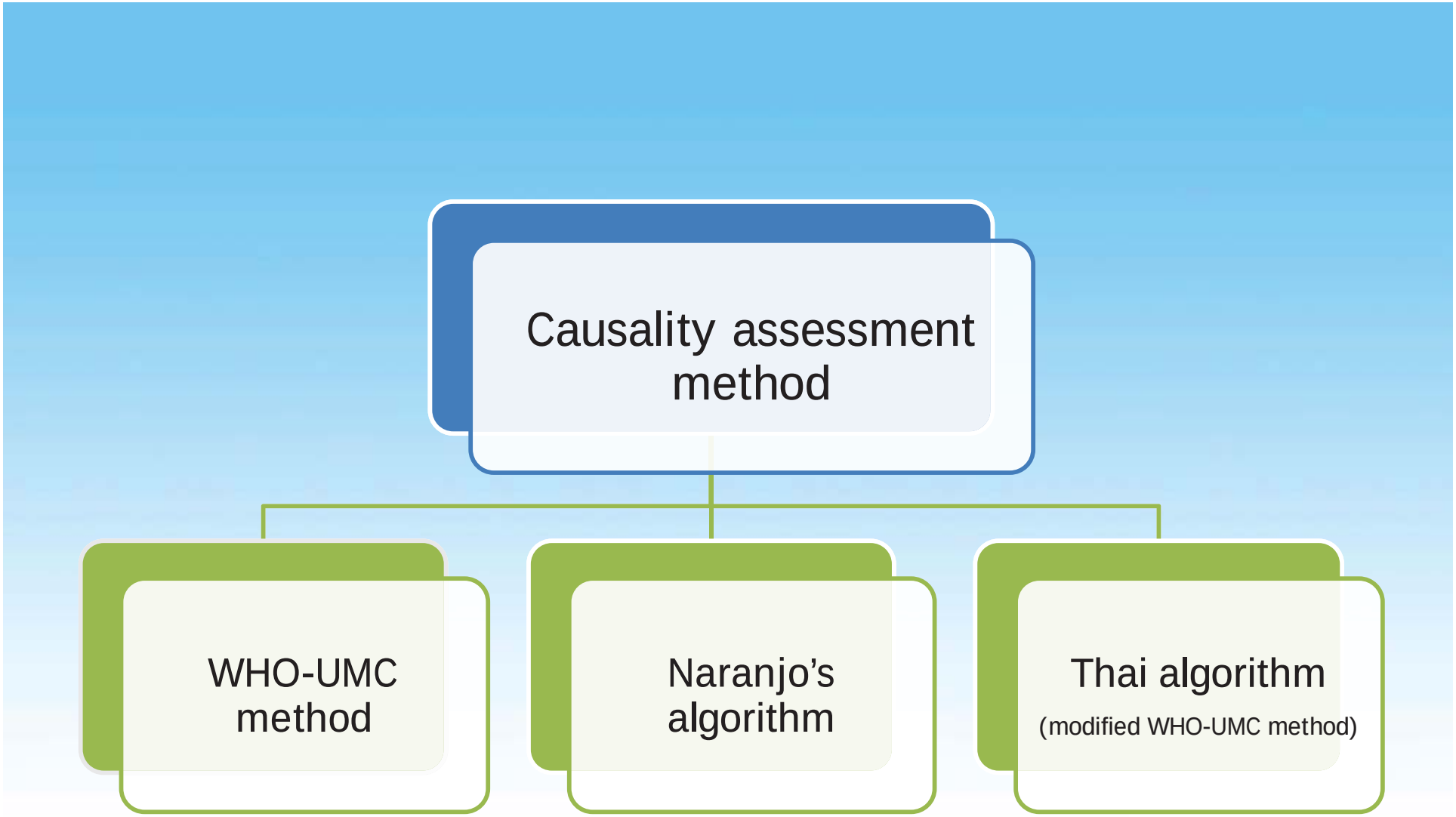


Risk minimization measures .
Warning message

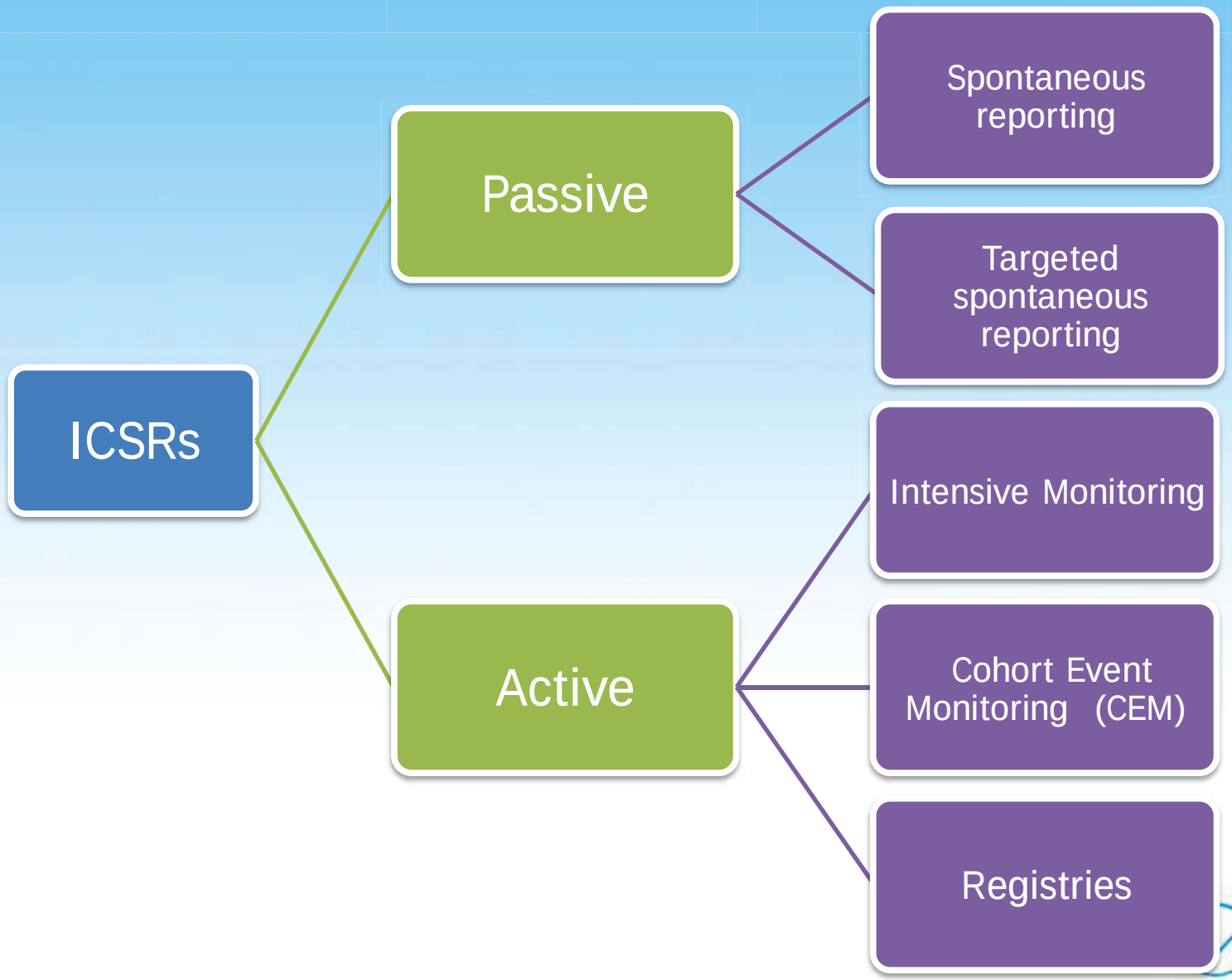
Dispensing program



Patient bed


Causality assessment method
WHO-UMC method
Naranjo's algorithm
Thai algorithm
(modified WHO-UMC method)

Surveillance methods utilized in PV

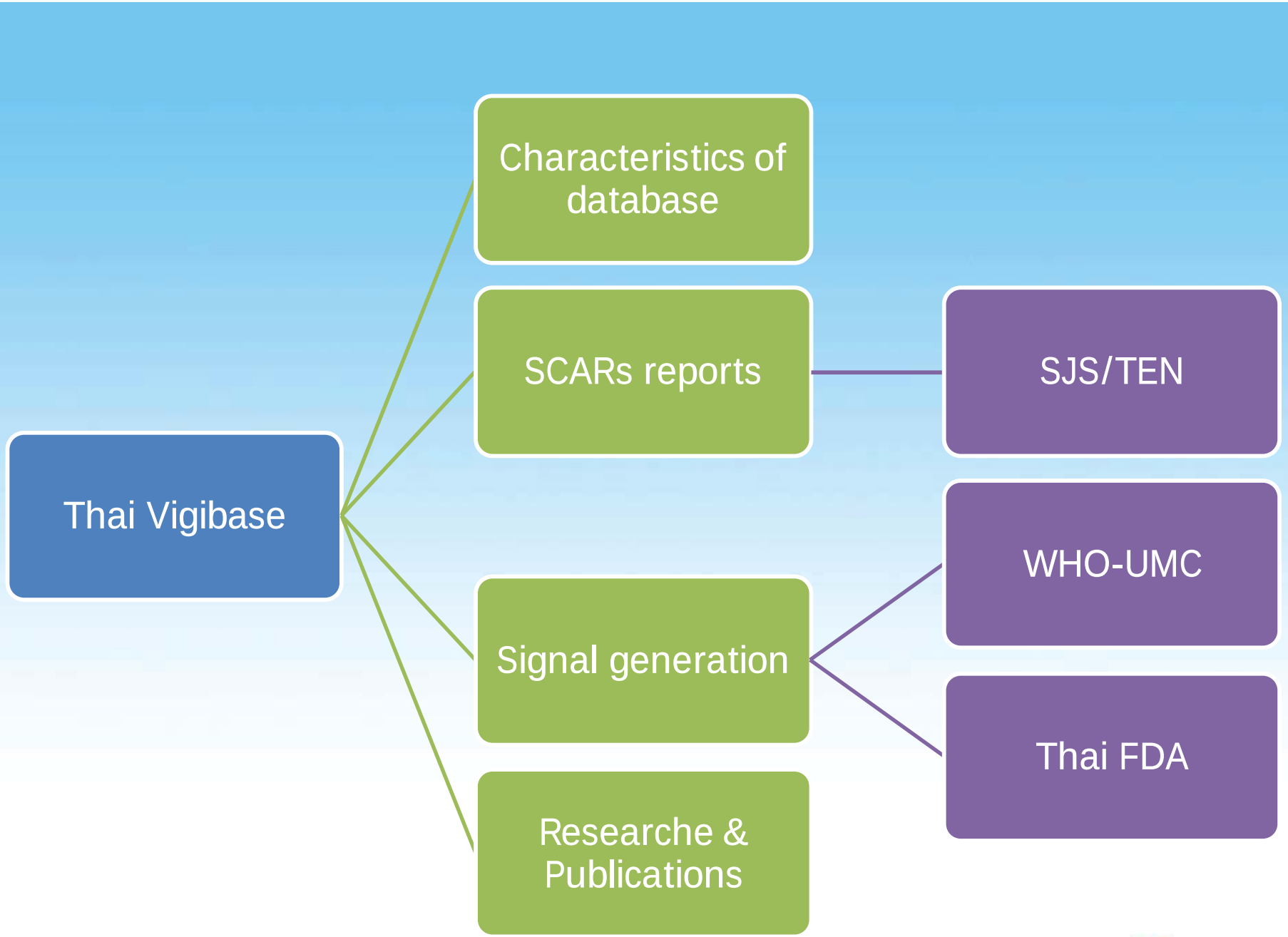


Passive Surveillance Methods

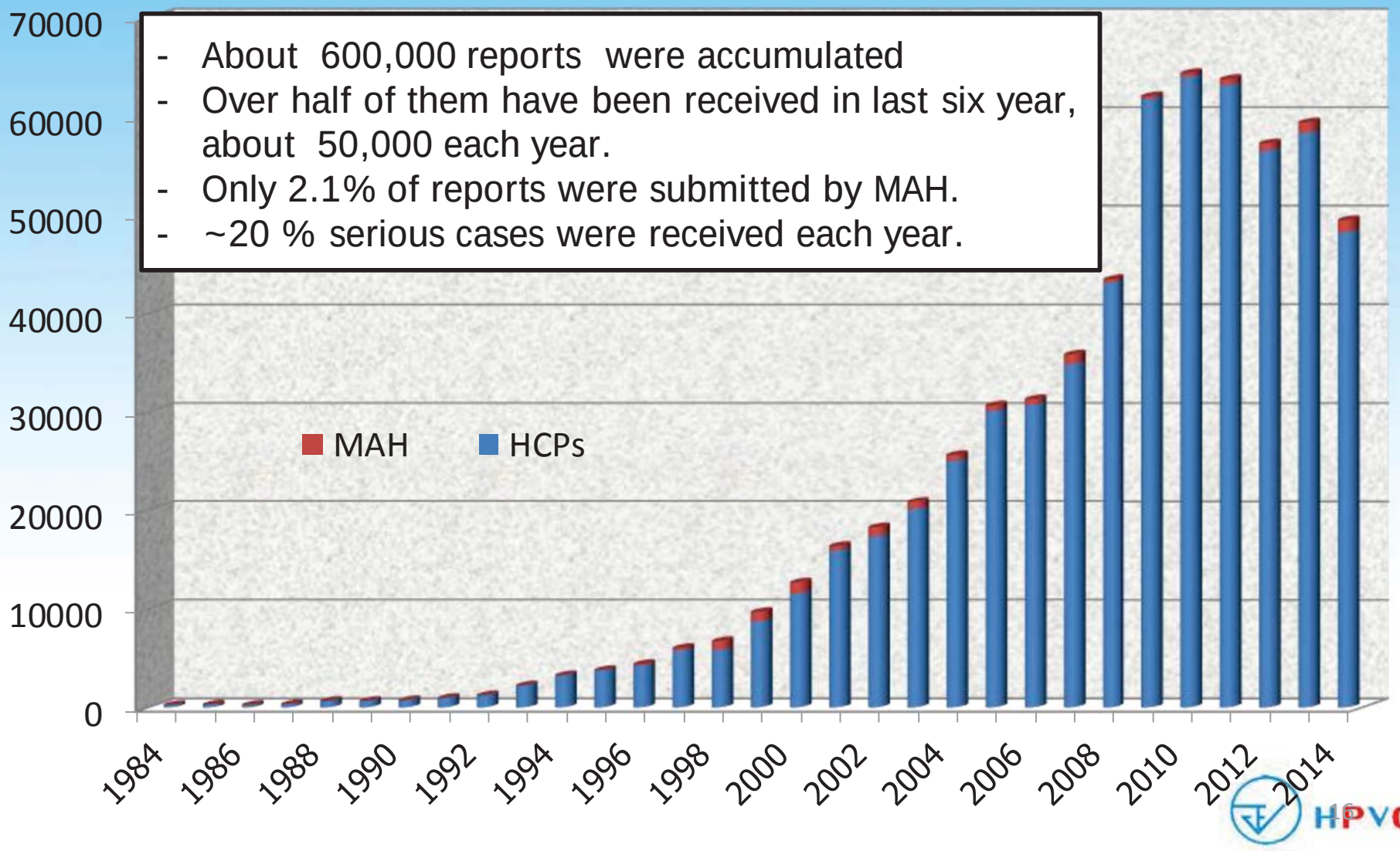
- Spontaneous reporting
  - Main method for all health product
    - Medicine including traditional medicine
    - Biological product including vaccine
- Targeted spontaneous reporting
  - Conditional approval new drug :
    - Safety Monitoring Program(SMP)
  - Herbal medicine in NEDL
  - Medicine use in public health program
    - Anti-TB dug, ARV

Active Surveillance Methods

- Intensive (hospital) monitoring
  - Product of interest
    - New drug , High alert drug
- Cohort event monitoring (CEM) : start 2015/16
  - Anti -TB drug
    - new drug , new regimen
- Registry
  - Thai EPO registry


Thai Vigibase
Characteristics of database
SCARs reports
SJS/TEN
Signal generation
WHO-UMC
Thai FDA
Researche & Publications

Number of reports by year in Thai Vigibase (1984-2014.)

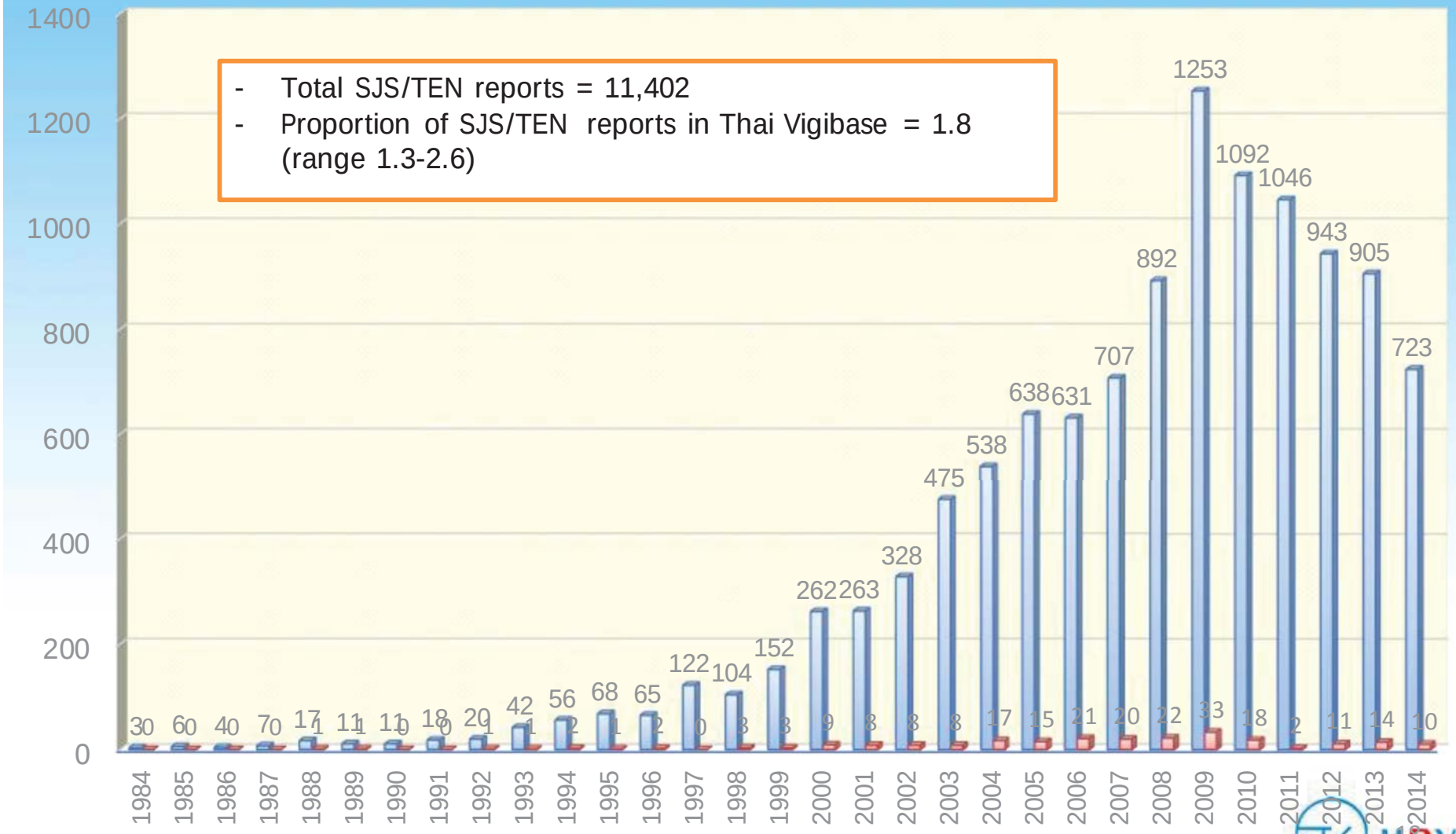


Number of SCARs Reports

(1984-2014)

SCARs	No. (%) [n = 18,896 reports 19,080 reactions]
Stevens Johnson Syndrome (SJS)	12,162 (63.7)
Erythema Multiforme (EM)	4,817 (25.2)
Toxic Epidermal Necrolysis (TEN)	1,282 (6.7)
DRESS Syndrome	504 (2.6)
Epidermal Necrolysis	315 (1.7)

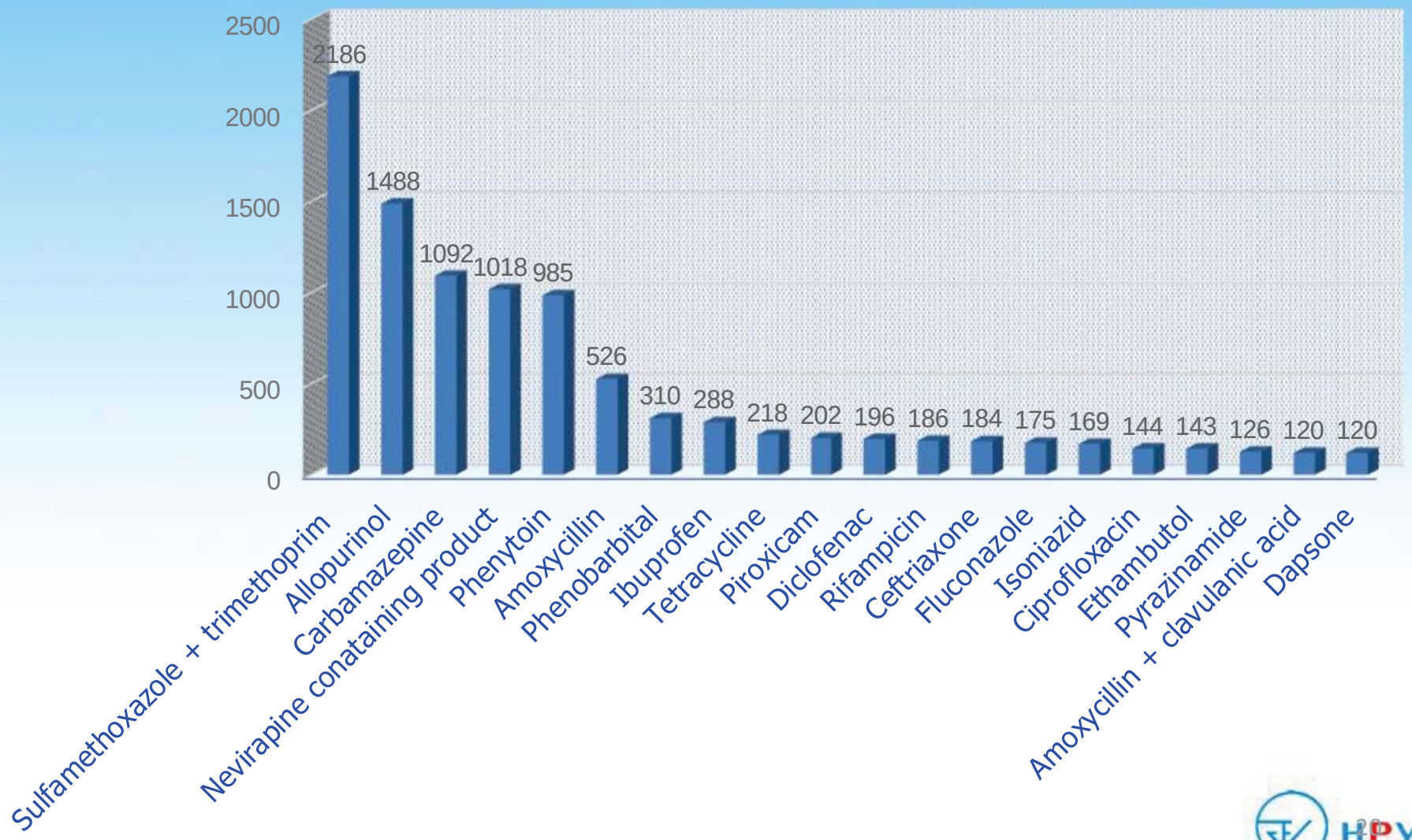
Number of SJS/TEN reports by year in Thai Vigibase (1984-2014)



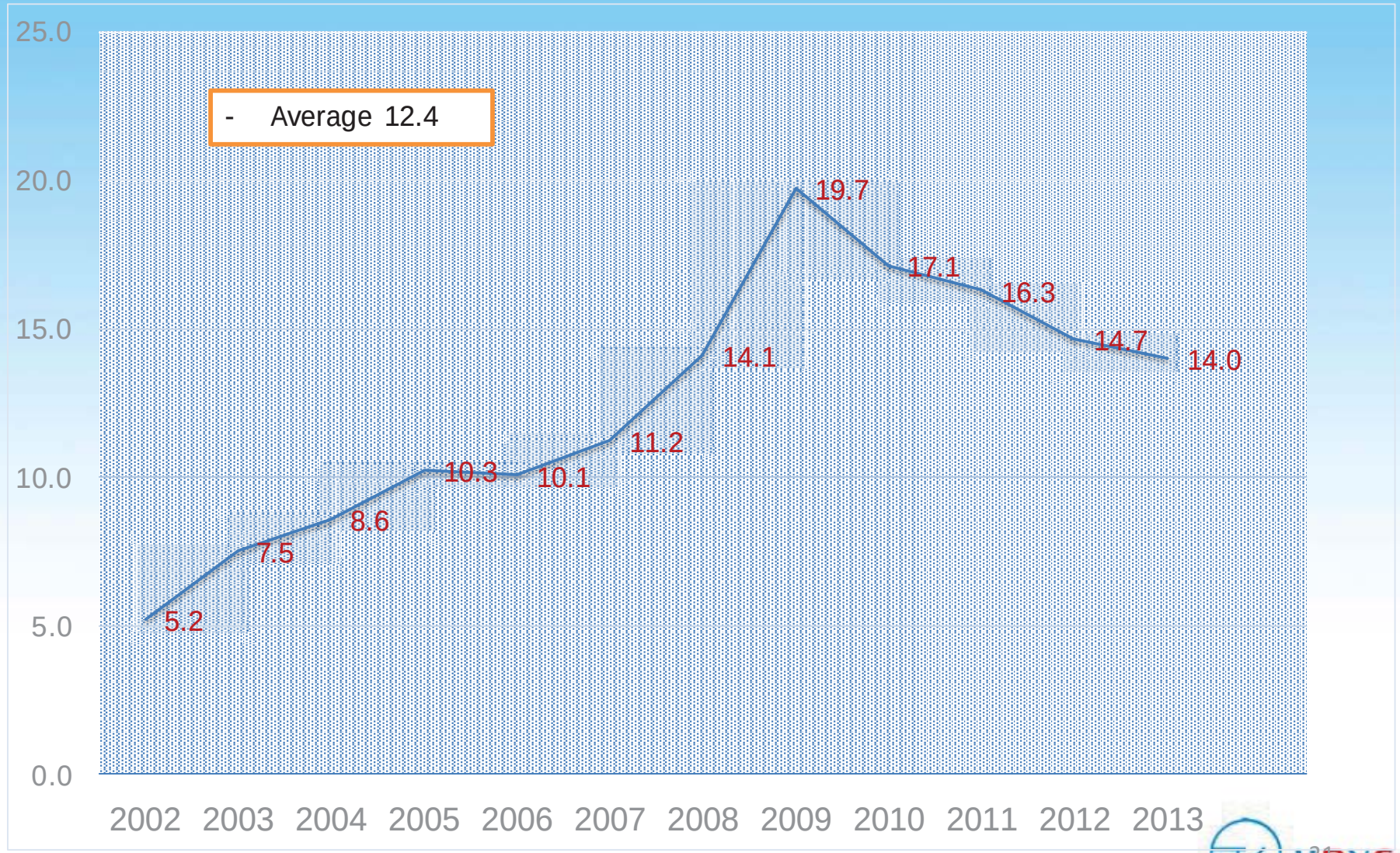
Characteristics of SJS/TEN Reports
(1984-2014)

Characteristics	No. (%) [n = 11,402 reports 11,457 reactions]
Sex	
• Female/Male	5,898 (51.7)/5,470 (48.0)
Age	
• <15	817 (7.2)
• 15-30	1,762 (15.5)
• 31-45	3,140 (27.5)
• 46-60	2,136 (18.7)
• > 60	2,615 (22.9)
Causality assessment	
• Certain	711 (6.2)
• Probable	7,636 (67.0)
• Possible	2,918 (25.6)
• Unlikely	22 (0.2)
• Unclassified/ unassessable	115 (1.0)
Death outcome	231 (2.0)

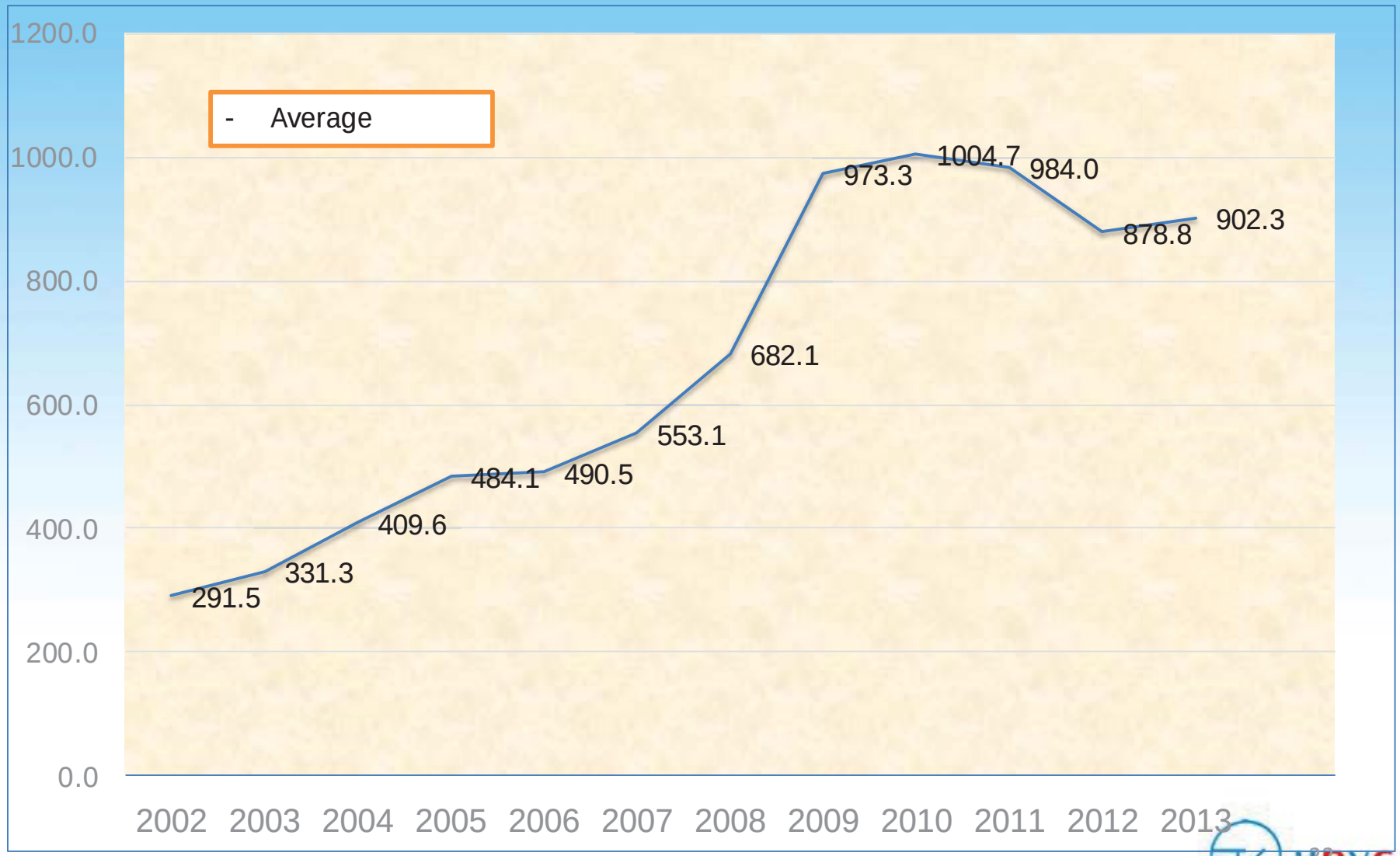
Most suspected drug & SJS/TEN
(1984-2014)



SJS-TEN Cases/ 1,000,000 Mid year population Thailand (2002-2013)



Total ADR Cases/ 1,000,000 Mid year population Thailand (2002-2013)



Signal Generation : WHO

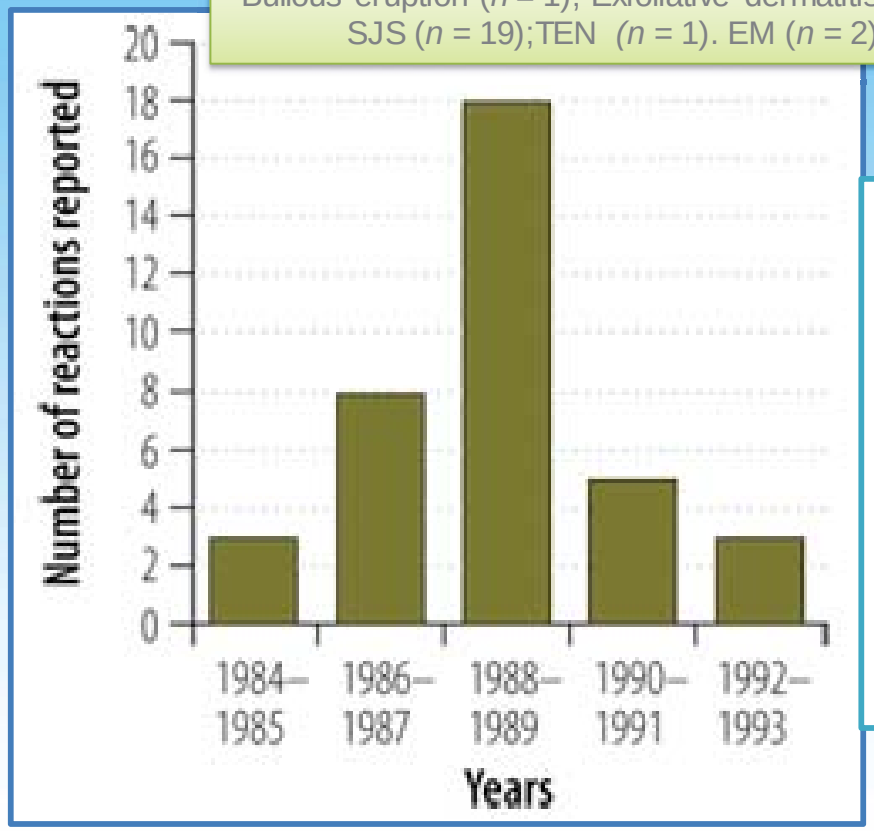
- Rifater (Isoniazid+ Rifampicin +Pyrazinamide) : dyspnoea (1/3)
  - WHO SIGNAL April 1997
- Arthemether : severe headache (9/10)
  - WHO SIGNAL April 2001
- Colchicine : Stevens-Johnson syndrome (8/23)
  - WHO SIGNAL September 2002
- Nitrates : EM, SJS and/or Epidermal necrolysis (1/61)
  - WHO SIGNAL June 2002
- Propylthiouracil : SJS (5/12) , EM (5/15) and Epidermal necrolysis (4/5)
  - WHO Newletter No2 2013

Signal Generation : Thai FDA

- Cassia siamea (leaf) ใบขี้เหล็ก : hepatic injury (2000)
  - Voluntary withdrawal
- Increase frequency of PRCA associated with EPO (2004-2005)
  - Thai EPO Registry
- Hypersensitivity reactions : *Andrographis paniculata (ฟ้าทะลายโจร)* containing drugs (2012-3)
  - HPVC Safety News
- Streptomycin : Steven-Johnson syndrome (2013)
  - Aminoglycoside - legal warning
- Eperisone : Anaphylactic reaction (2013)
  - HPVC safety News

Reported cutaneous hypersensitivity reactions associated with thioacetazone, Thailand, 1984–1993

Bullous eruption (*n* = 1); Exfoliative dermatitis (*n* = 4); SJS (*n* = 19);TEN (*n* = 1). EM (*n* = 2);



- These reports are consistent with the publications from Africa.
  - An increased risk of severe cutaneous reactions associated with the use of thioacetazone in persons with HIV infection.
- It is notable that the timing of the reporting peak coincides with the evolution of the HIV epidemic in Thailand

Ref. Pharmacovigilance and tuberculosis: applying the lessons of thioacetazone
WHO Bulletin 2014;92:918-919.

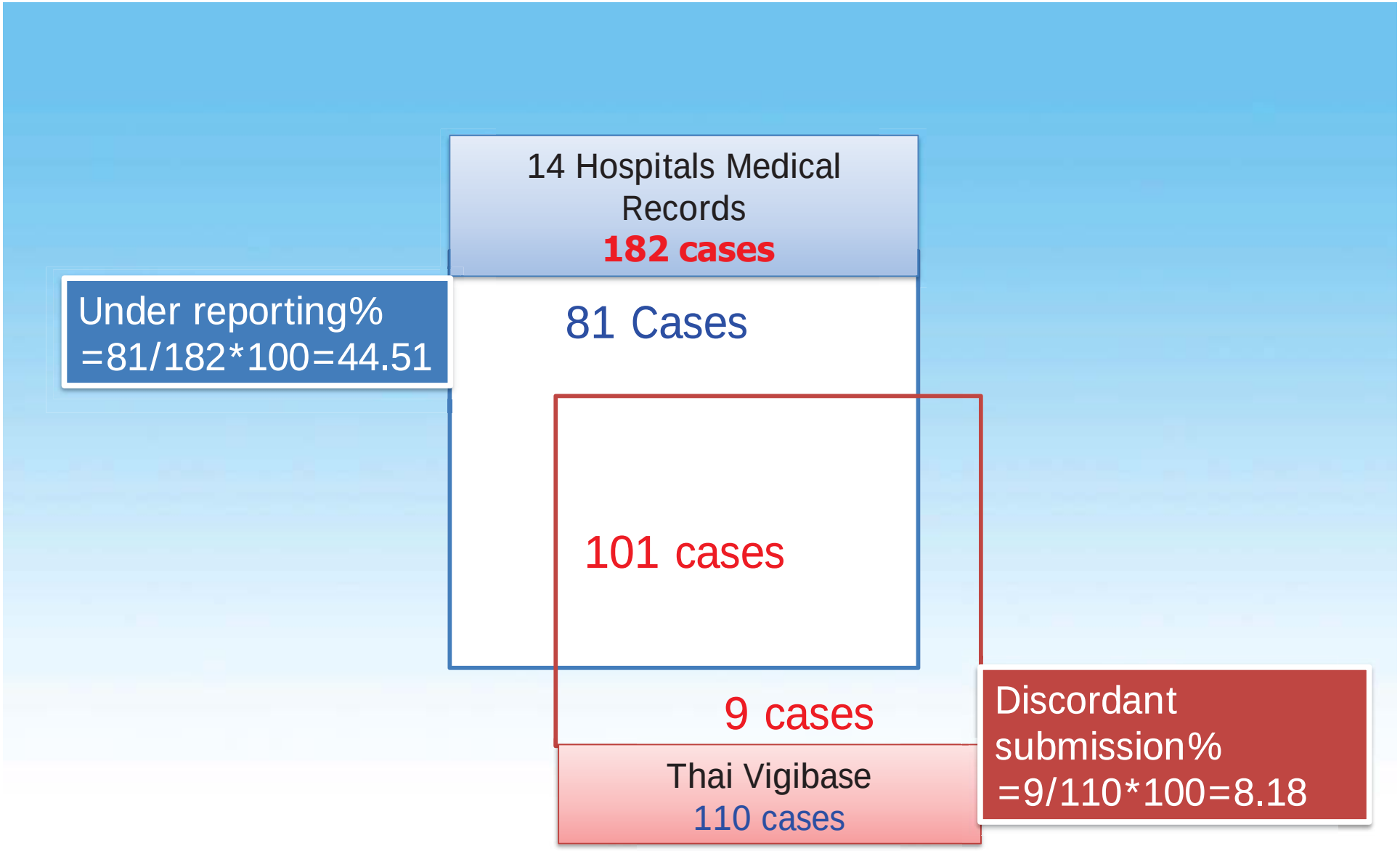
Researches & Publications

using Thai Vigibase

Evaluation on reporting serious adverse drug reactions in Thai SRS: a case study of SJS and TEN

Thesis by Wittaya Prachachalerm

- Research design
  - Cross-sectional design
- Research setting:
  - 14 selected hospitals from five regions of Thailand
- Compared cases in 2005
  - Thai Vigibase
  - 14 selected hospitals
    - Retrieved by using ICD-10 computerized system
    - Verified with patient medical records


14 Hospitals Medical Records
182 cases
Under reporting%
=81/182*100=44.51
81 Cases
101 cases
9 cases
Thai Vigibase
110 cases
Discordant submission%
=9/110*100=8.18

Publications-1

- Detection of Adverse Drug Reaction Signals in the Thai FDA Database : Comparison Between Reporting Odds Ratio and Baysian Conference Propagation Neural Networks Methods.
  - Drug Information Journal: 2010;44(4):393-403.
- Safety of Herbal Products in Thailand An Analysis of Reports in the Thai Health Product Vigilance Center Database from 2000 to 2008”
  - Drug Safety: 2011; 34 (4): 339-350.
- Characterization of Statin-Associated Myopathy Case Reports in Thailand Using the Health Product Vigilance Center Database”
  - Drug Safety: 2013; 36 (2): 583-.591

HPVC

Publications-2

- Signal detection for Thai traditional medicine: Examination of national pharmacovigilance data using reporting odds ratio and reported population attributable risk.
  - Regulatory Toxicology and Pharmacology, Volume 70, Issue 1, October 2014, Pages 407-412, ISSN 0273-2300
- Characterization of Hypersensitivity Reactions Reported among *Andrographispaniculata* Users in Thailand Using Health Product Vigilance Center (HPVC) Database.
  - BMC Complementary and Alternative Medicine:2014,14:515
- Renin Angiotensin System Blockers associated Angioedema among Thai Population: Analysis from Thai National Pharmacovigilance Database.
  - Accepted by Asia Pacific Journal of Allergy and Immunology (AJPAI)

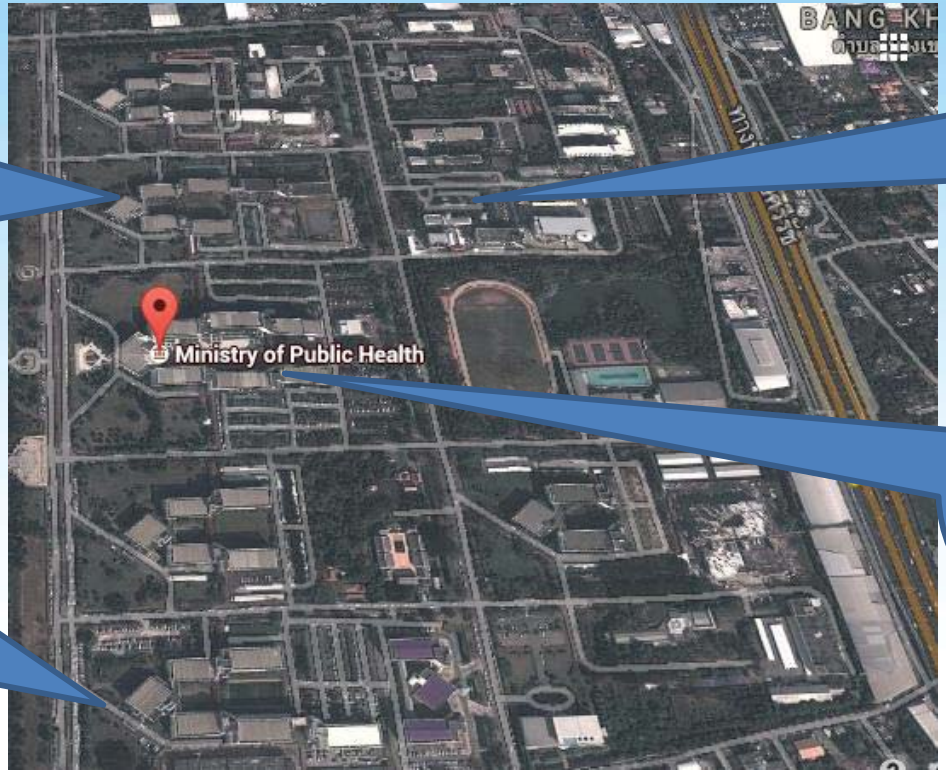
HPVC

PV & PGx Research

DMSC, Thai FDA, Hospitals in MOPH

HITAP, Health economic evaluation unit

Thai FDA, Health Product Vigilance Center



DMSc (10 buildings, 12 regional centers

Permanent secretary office, 800 hospitals centers

HPVC

26th August 2009 (BrainSTROMING)

Thailand PharmacoGenomics Network (TPGN)

75 likes · 3 talking about this

Update Page Info | Liked | Following

(www.thailandpg.org, www.facebook.com/ThailandPGx)

Local Business

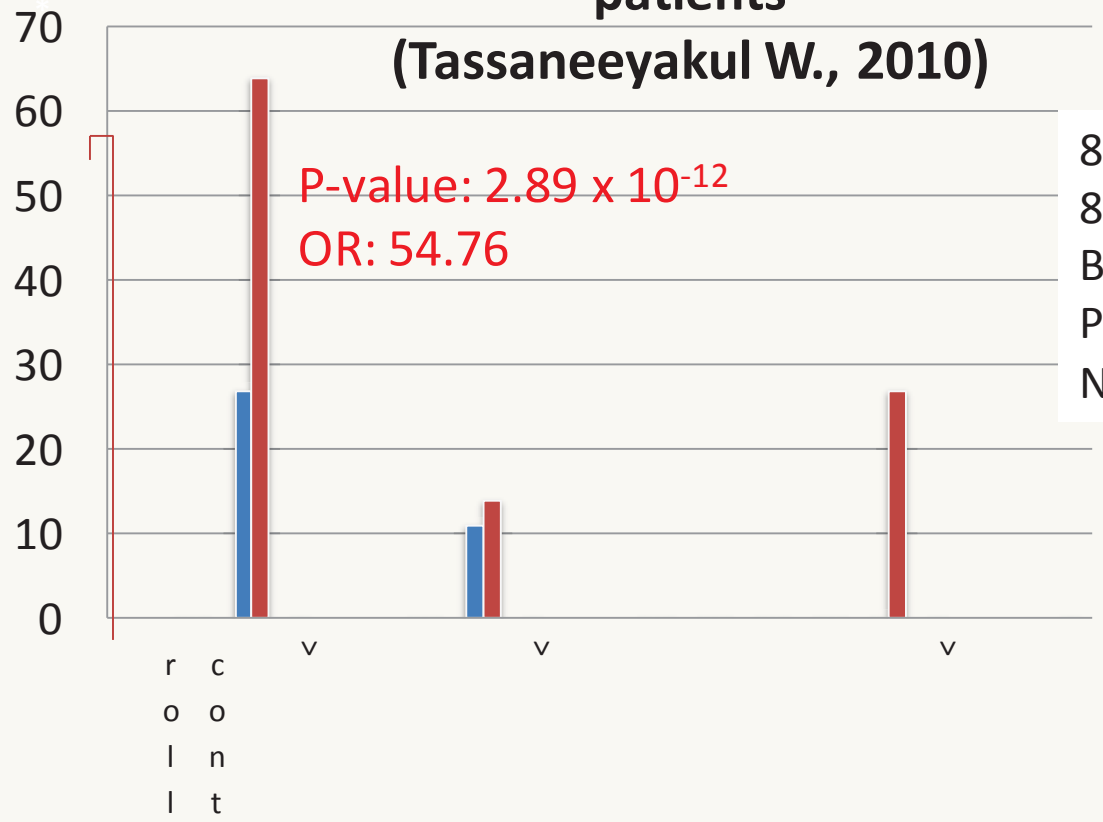
National Institute of Health, Department of Medical Sciences, Ministry of Public ...

02 951 0000 ext. 98096

75

HPVC

Frequencies of certain HLA-B alleles in CBZ-induced SJS/TEN versus CBZ tolerant patients (Tassaneeyakul W., 2010)

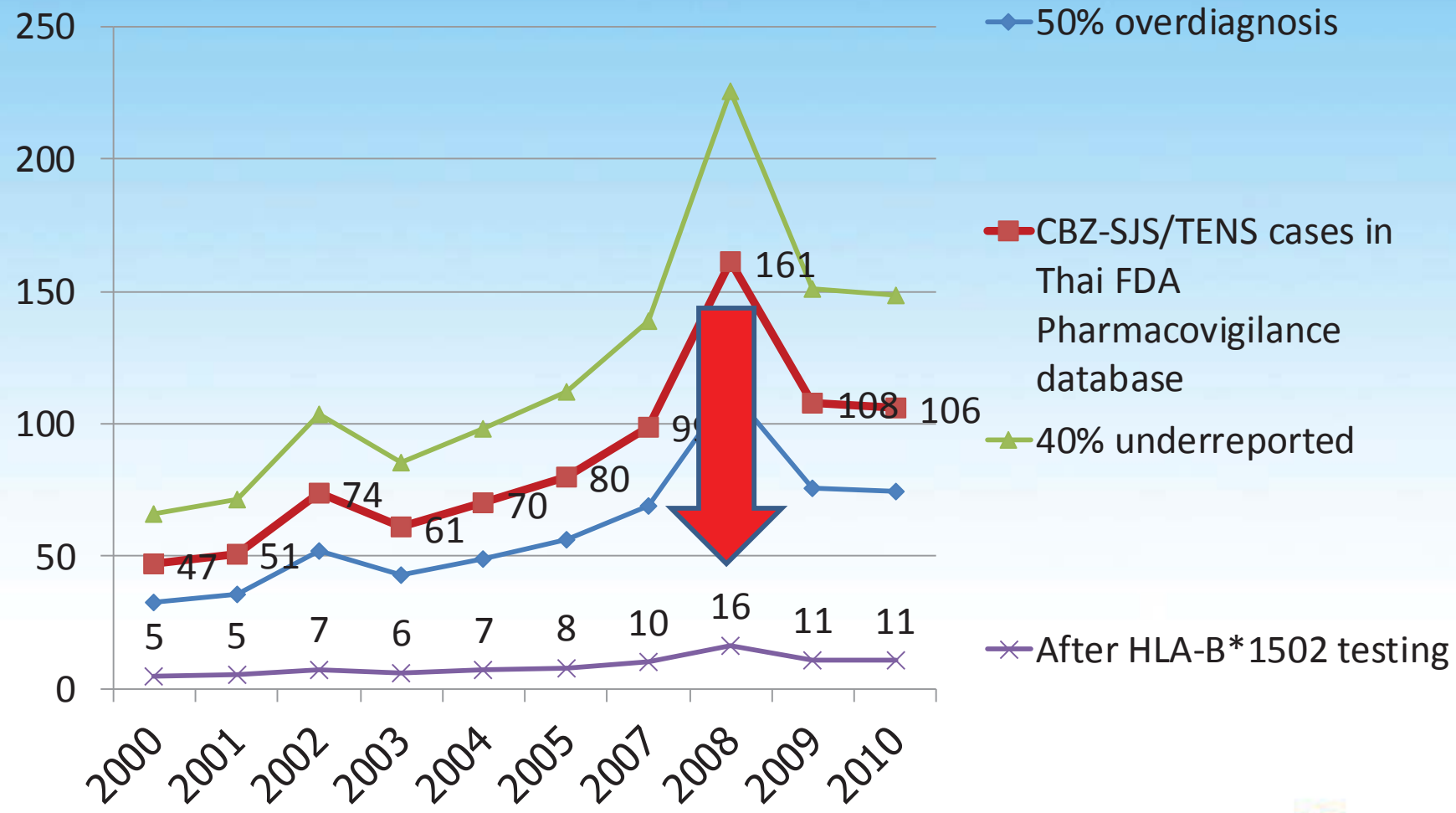


88.7 % sensitivity
88.7 % specificity
Based risk (2.9/1000)
PPV 1.92% (1/50)
NPV 99.96% (2/1000)

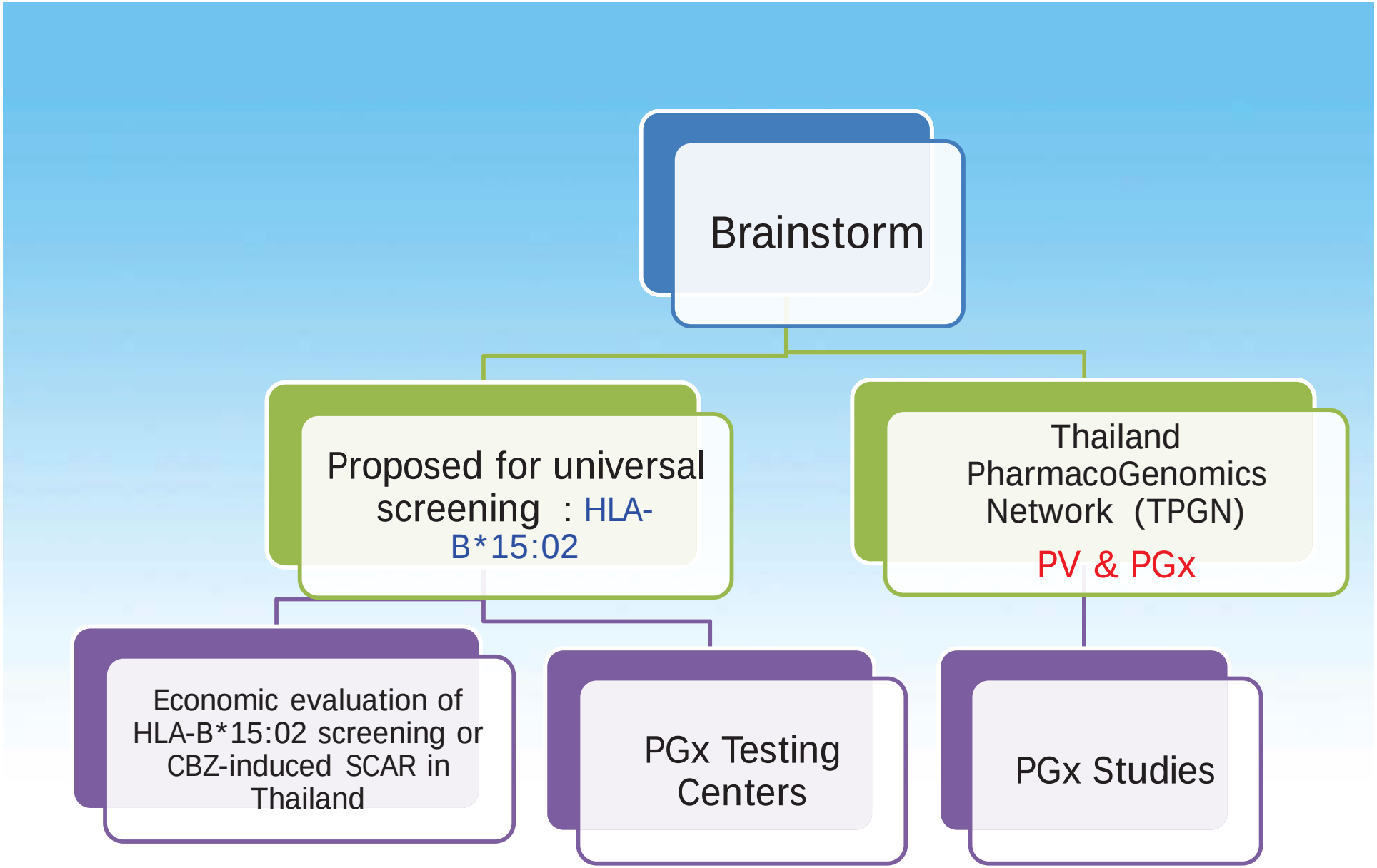
Ref: Association between HLA-B*1502 and Carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia 2010, 51(5): 926-930*

HPVC

~90% of CBZ-SJS/TEN is preventable by preventative test of HLA-B*15:02



HPVC


Brainstorm
Proposed for universal screening : HLA-B*15:02
Thailand PharmacoGenomics Network (TPGN)
PV & PGx
Economic evaluation of HLA-B*15:02 screening or CBZ-induced SCAR in Thailand
PGx Testing Centers
PGx Studies

Epilepsia, 54(9):1628–1638, 2013
doi: 10.1111/epi.12325

FULL-LENGTH ORIGINAL RESEARCH

Economic evaluation of HLA-B*15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand

*Waranya Rattanavipapong, *Tanunya Koopitakkajorn, *†Naiyana Praditsitthikorn, ‡Surakameth Mahasirimongkol, and *Yot Teerawattananon

*Health Intervention and Technology Assessment Program (HITAP), Nonthaburi, Thailand; †Bureau of AIDS TB and STIs, Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand; and ‡The National Institute of Health, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand

SUMMARY

Purpose: There is strong evidence of an association between the presence of the human leukocyte antigen (HLA)-B*15:02 and two severe adverse drug reactions—Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)—in patients taking carbamazepine (CBZ), a common treatment for patients with epilepsy and neuropathic pain. As a result, there are calls for all patients that are due to undergo CBZ therapy to be screened for this genetic marker before commencing their therapy. This study aims to determine the value for money of HLA-B*15:02 screening compared to the following: (1) administering CBZ therapy without conducting patient screening, and (2) not prescribing CBZ but alternative drugs that are less likely to result in severe reactions, but that come at a higher cost.

Method: An economic evaluation was carried out by using a decision tree and Markov models to examine the cost-utility of providing HLA-B*15:02 screening for all patients with either newly diagnosed epilepsy or neuropathic pain in the Thai setting. All transitional probabilities were derived from the national and international literature. The majority of the data on direct medical care costs were collected from 10 community, provincial, and regional hospitals throughout Thailand. Direct non-medical cost and health-related quality of life (HRQoL) data were obtained from interviews that were conducted with 33 patients, some of whom had experienced severe drug reactions.

Key Findings: The incremental cost-effectiveness ratio (ICER) of adopting a universal HLA-B*15:02 screening policy was estimated at 222,000 Thai baht, THB/quality-adjusted life year (QALY) gained for epilepsy patients and 130,000 THB/QALY gained for patients with neuropathic pain. Furthermore, we found that 343 patients need to be tested for HLA-B*15:02 allele to prevent one case of SJS/TEN.

Significance: Universal HLA-B*15:02 screening represents good value for the money in terms of preventing SJS/TEN in CBZ-treated patients with neuropathic pain at the Thai ceiling ratio of 120,000 THB/QALY gained. However, the prevalence of CBZ-induced SJS/TEN in the Thai population and the positive predictive value (PPV) are major factors that influence the cost-effectiveness of HLA-B*15:02 screening. Therefore, an active surveillance system to make a more accurate assessment of the prevalence CBZ-induced SJS/TEN in the Thai population would enhance the generalizability of the results.

KEY WORDS: Cost-utility analysis, HLA-B*15:02, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

According to national and global pharmacovigilance systems, the most common adverse drug reactions (ADRs) are cutaneous. The most severe life-threatening forms of cutaneous ADRs are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), two related acquired bullous disorders of the skin that, in the majority of cases, are caused by reactions to certain drugs, such as sulfonamide-antibiotics, antiepileptic agents—especially carbamazepine (CBZ), allopurinol, and oxicam-type nonsteroidal antiinflammatory drugs (NSAIDs) (Harr & French, 2010). Incidence rates for SJS/TEN vary according to ethnicity, and the highest rates are seen among Han Chinese, Malays, and Thais (Lim et al., 2008).

CBZ is the primary treatment choice for patients with epilepsy and neuropathic pain according to current Thai

Accepted June 18, 2013; Early View publication July 29, 2013.
Address correspondence to Naiyana Praditsitthikorn, Department of Health, Health Intervention and Technology Assessment Program (HITAP), Ministry of Public Health, 6th Floor, 6th Building, Tiwanon Road, Muang, Nonthaburi 11000, Thailand. E-mail: naiyana.p@hitap.net

Wiley Periodicals, Inc.
© 2013 International League Against Epilepsy

Economic evaluation of HLA-B*15:02 screening or CBZ-induced SCAR in Thailand

Dr. Waranya Rattanavipapong
(HITAP)

AT QALY 120,000 Baht
(4000 USD)

Testing for Neuropathic pain is cost effective

Testing for Epilepsy is borderline cost effective

HPVC

Location of regional medical science centers providing PGx testing in MOPH (9 centres)

1. ฝ่ายพันธุศาสตร์การแพทย์ สถาบันวิจัยวิทยาศาสตร์สาธารณสุข
   โทร. 02-2951-0000 ต่อ 98096, 99140 Nonthaburi
2. ศูนย์วิทยาศาสตร์การแพทย์ ขอนแก่น Khonkaen
3. ศูนย์วิทยาศาสตร์การแพทย์ อุดรธานี Udonthani
4. ศูนย์วิทยาศาสตร์การแพทย์ พิษณุโลก Phitsanulok
5. ศูนย์วิทยาศาสตร์การแพทย์ นครสวรรค์ Nakornsawan
6. ศูนย์วิทยาศาสตร์การแพทย์ สมุทรสงคราม Samutsonkarm
7. ศูนย์วิทยาศาสตร์การแพทย์ ตรัง Trang
8. ศูนย์วิทยาศาสตร์การแพทย์ สงขลา Songkla
9. ศูนย์วิทยาศาสตร์การแพทย์ เชียงราย Chiangrai

HPVC

เลือด
(EDTA-blood)

หรือ

เซลล์เยื่อบุกระพุ้งแก้ม
(Buccal cells by cytology brush)

3 days guaranteed turn around time

DNA extraction

DNA

Multiplex allele specific PCR

HPVC

Nation-WIDE PGx SERVICE Announcement

07/06/2012

กรมวิทย์พัฒนาเทคนิตตรวจสารพันธุกรรมป้องกันการแพ้ยา

Pilot free testing for all CBZ prescribed in Bangkok

3/10/2013

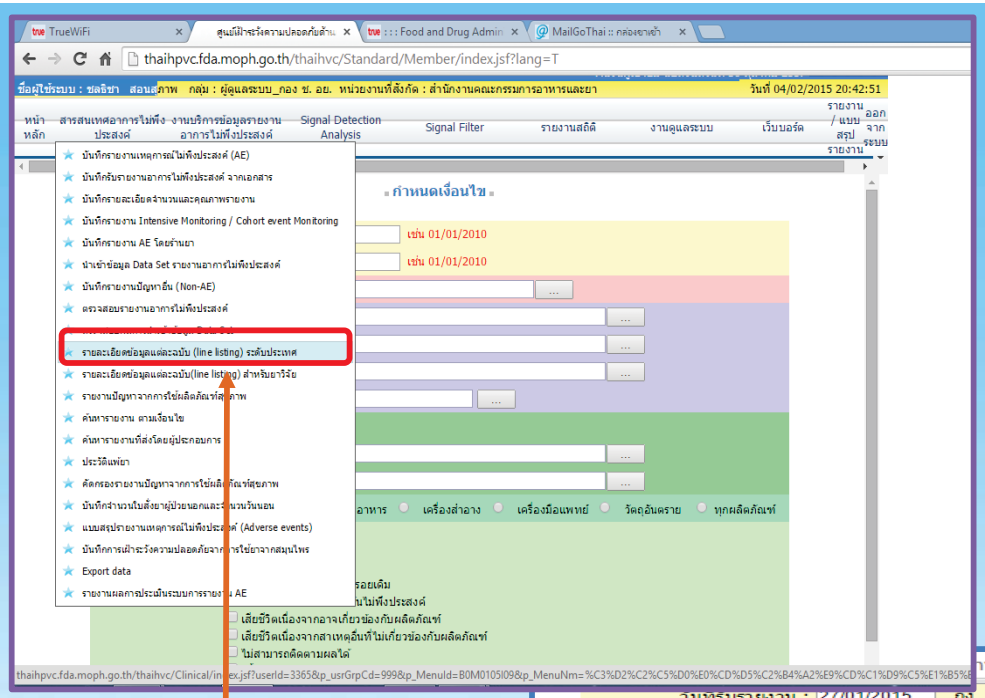
HPVC

18 Hospitals participated in ThaiSCAR-PGx Phase I study

1. รพ. เลิดสิน	กรุงเทพ
2. สถาบันสุขภาพเด็กแห่งชาติมหาราชินี	
3. สถาบันโรคผิวหนัง	
4. รพศ. อุดรธานี	อุดรธานี
5. รพ. เชียงรายประชานุเคราะห์	เชียงราย
6. รพ. สกลนคร	สกลนคร
7. รพ. ลำปาง	ลำปาง
8. รพ. พุทธชินราช	พิษณุโลก
9. รพ. หาดใหญ่	สงขลา
10. รพ. สงขลา	
11. รพ. สระบุรี	สระบุรี
12. รพ. มหาราชนครราชสีมา	นครราชสีมา
13. รพ. ขอนแก่น	ขอนแก่น
14. รพ. พระนครศรีอยุธยา	อยุธยา
15. รพ. อ่างทอง	อ่างทอง
16. รพ. สรรพสิทธิประสงค์	อุบลราชธานี
17. รพ. สุราษฎร์ธานี	สุราษฎร์ธานี
18. รพ. ระยอง	ระยอง

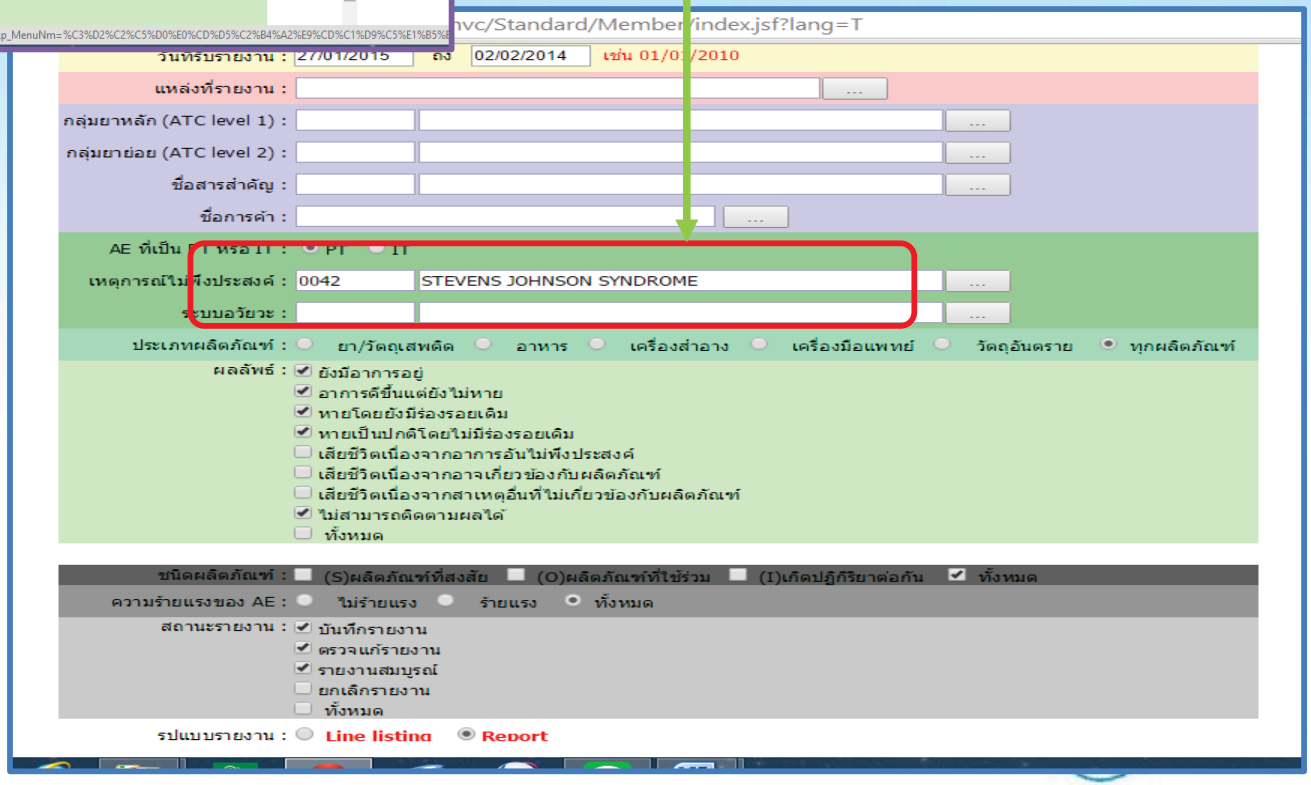
HPVC

How to detect cases for the research ?

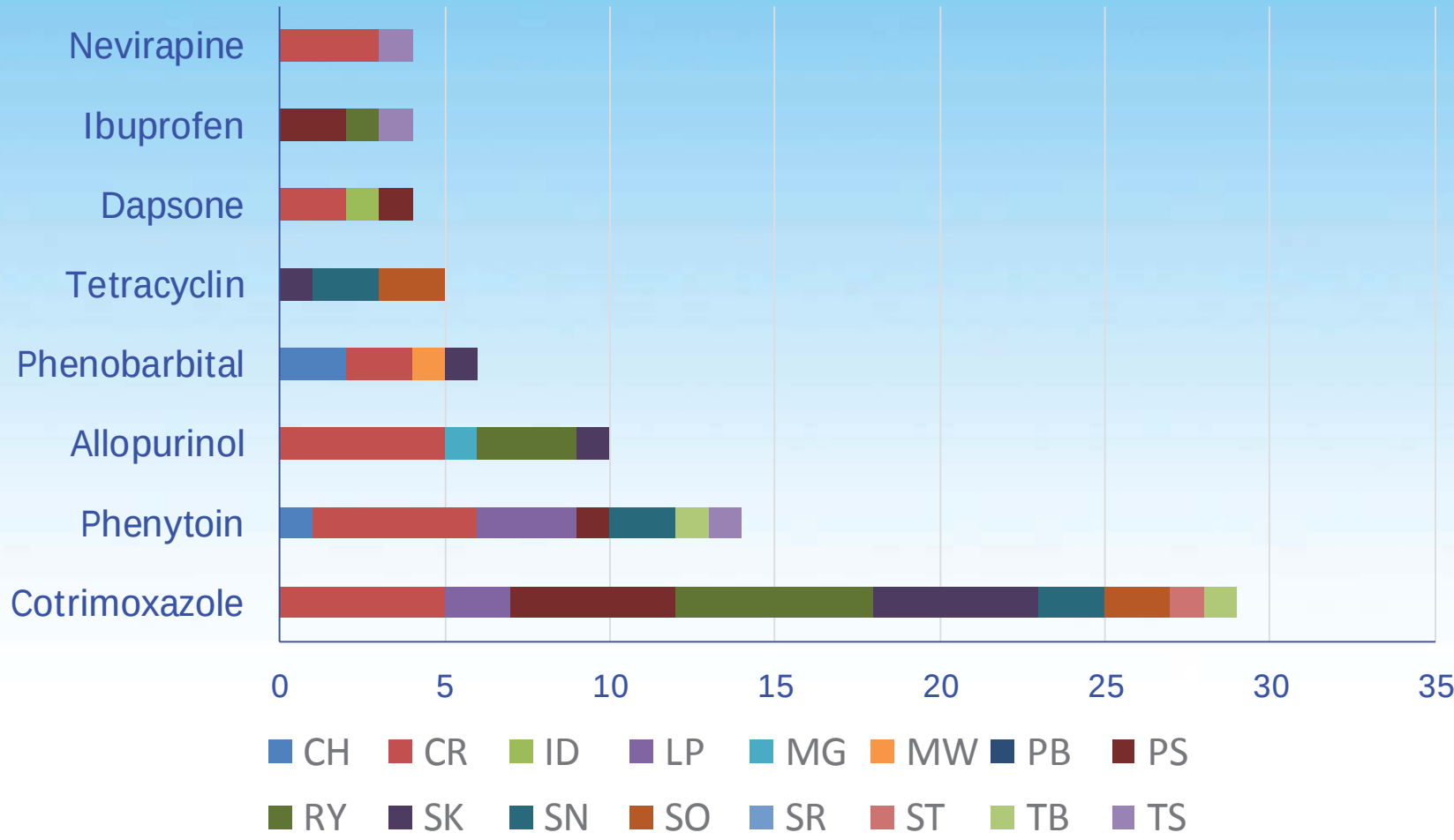


Line listing menu

Search term: SJS

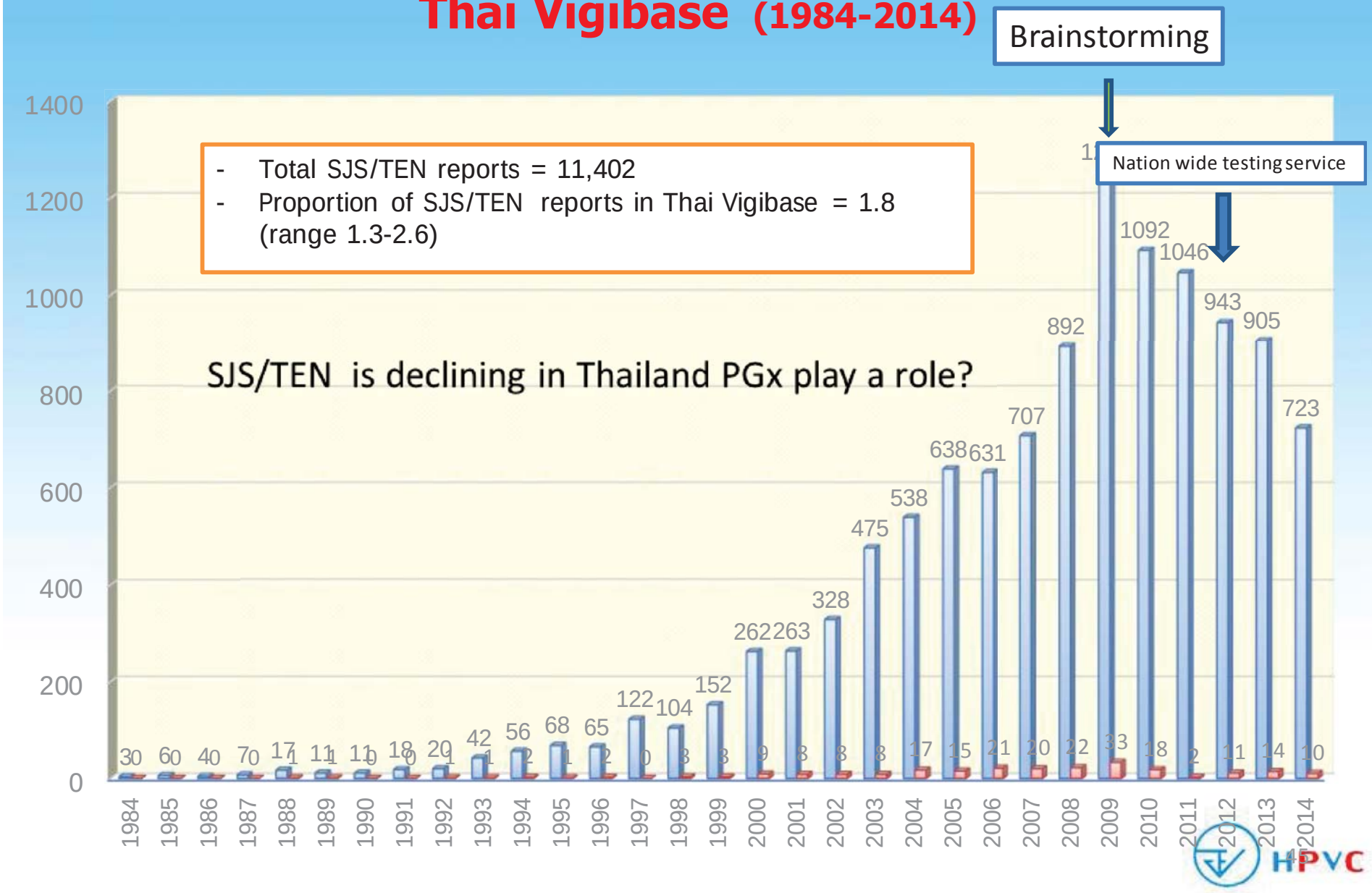


Number of DNA samples collected based on suspected drug (2012-2014)



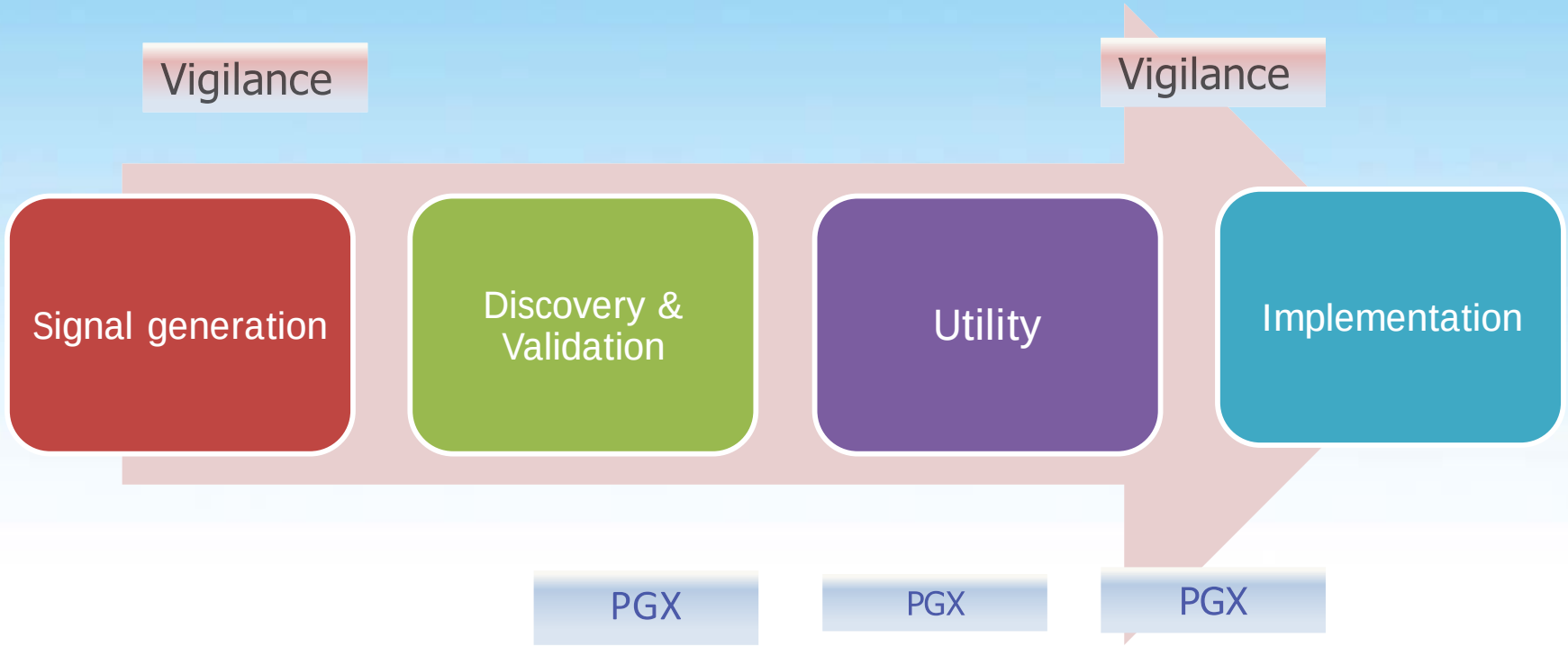
HPVC

Number of SJS/TEN reports by year in Thai Vigibase (1984-2014)



HPVC

PGx & PV:
Partnership for Patient Safety



HPVC

Acknowledgement

Dr. Surakameth Mahasirimongkol

Thank You.