



弭平重症診斷之地域差異： 以頑固性癲癇為例

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Childhood Epilepsy

Epilepsy is among the most common pediatric neurological disorders in need of long-term medication treatment.

About 50 million people worldwide have epilepsy, with an increased prevalence in childhood and adolescence.

Epilepsy in children is occasionally associated with variable comorbidities.

Diagnosis and treatment are challenges to pediatric neurologists.

Prevalence and Incidence: North America

- **Canada**

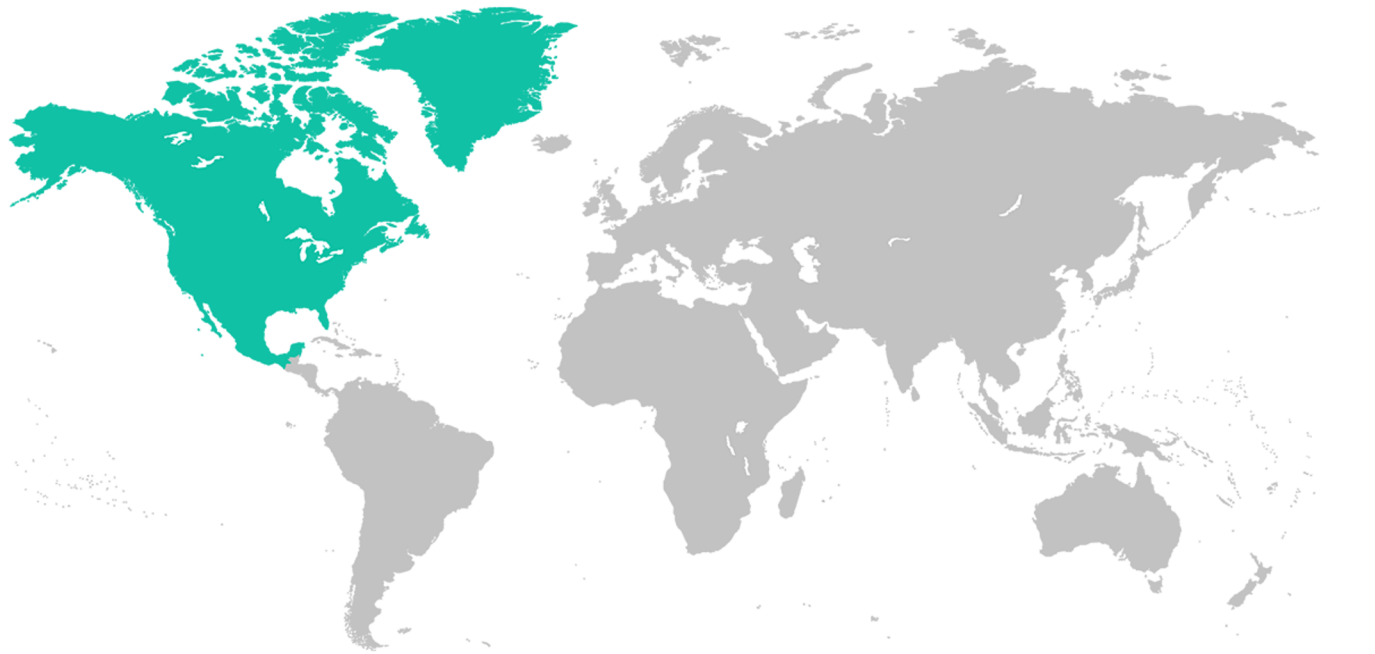
Prevalence: 5.26 / 1000

Incidence: 41 / 100,000

- **USA**

Prevalence: 6.8 / 1,000

Incidence: 104 / 100,000



Prevalence and Incidence: Africa and Mid East

Kenya (6-9y)

Prevalence: 11 / 1000

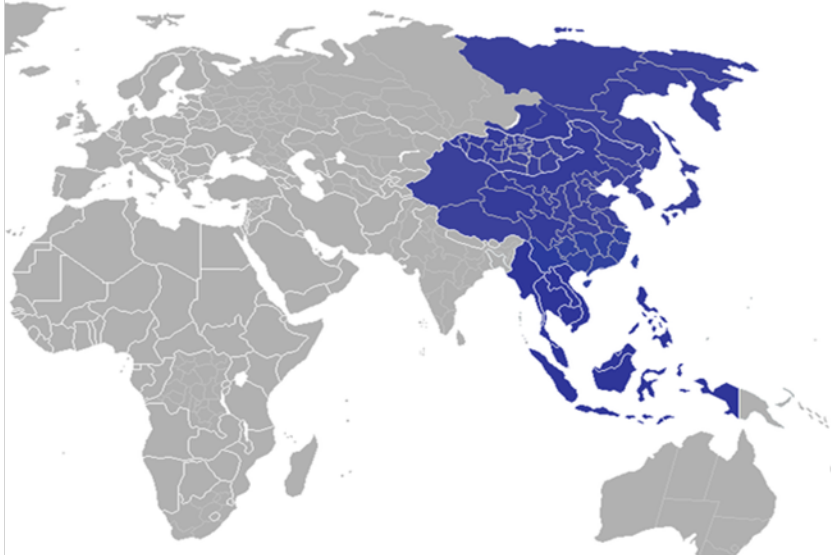
Incidence: 187 / 100,000

Saudi Arabia *(Al Rajeh et al., 2001)*

Prevalence: 6.5 / 1000



Asia – Japan, Hong Kong, and China



Hong Kong (1997)

Prevalence:
4.3 / 1000

China (2015)

Prevalence:
4.5 / 1000 (0-4y)
5.3 / 1000 (5-9y)
6.2 / 1000 (10-14y)
7.0 / 1000 (15-19y)

Japan

Prevalence: (2018)
5.3 / 1000
0.9 / 1000 (0y)
3.3 / 1000 (1-4y)
6.5 / 1000 (5-9y)
7.2 / 1000 (10-12y)

Incidence: (rural, 1999)
70.4 / 100,000
108 / 100,000 (1-4y)
38 / 100,000 (5-9y)
67 / 100,000 (10-14y)

E. Oka et al., *Epilepsia*. 2006 Mar;47(3):626-30.
Okamoto et al., *Brain Dev*. 2018 Nov;40(10):904-908.
Virginia Wong et al., *J Child Neurol*. 2004 Jan;19(1):19-25.
P. Song et al., *J Glob Health*. 2017 Dec; 7(2): 020706.

Prevalence and neuro-psychiatric comorbidities of pediatric epilepsy in Taiwan: A national population-based study

Kuo-Liang Chiang^a, Chen-Yang Cheng^{b,*}

Method:

Age < 20 y/o, diagnosis of epilepsy and epileptic seizures in 2005 were identified in the NHIRD based on ICD-9-CM and prescription records for the use of at least one AED

Findings:

- (1) Crude prevalence 3.3 / 1000 in 2005
- (2) Significantly higher in boys aged ≤ 4 years
- (3) Increasing epilepsy prevalence from urban to rural areas
- (4) Comorbidities are identified in 39.0%, most common : developmental delay, cerebral palsy, and mental retardation

Case-control population-based study in Taiwan

Characteristic	No.(%) of Individuals		P-value
	With EP n=2629	Without EP n=7887	
Comorbidity			
Depression	44(1.7)	24(0.3)	<0.001
Anxiety disorder	188(7.2)	104(1.3)	<0.001
Autism spectrum	25(1)	15(0.2)	<0.001
Conduct disorder	20(0.8)	12(0.2)	<0.001
Bipolar disorder	2(0.1)	1(0)	0.096
Sleep disorder	63(2.4)	52(0.7)	<0.001
Obsessive compulsive disord	8(0.3)	4(0.1)	<0.001
Learning difficulties	35(1.3)	12(0.2)	<0.001
Mental retardation	181(6.9)	39(0.5)	<0.001
Attention deficit disorder	200(7.6)	137(1.7)	<0.001
Migraine	78(3)	33(0.4)	<0.001

The problems faced in management of epilepsy in children

Unavailable new
treatments in
Taiwan

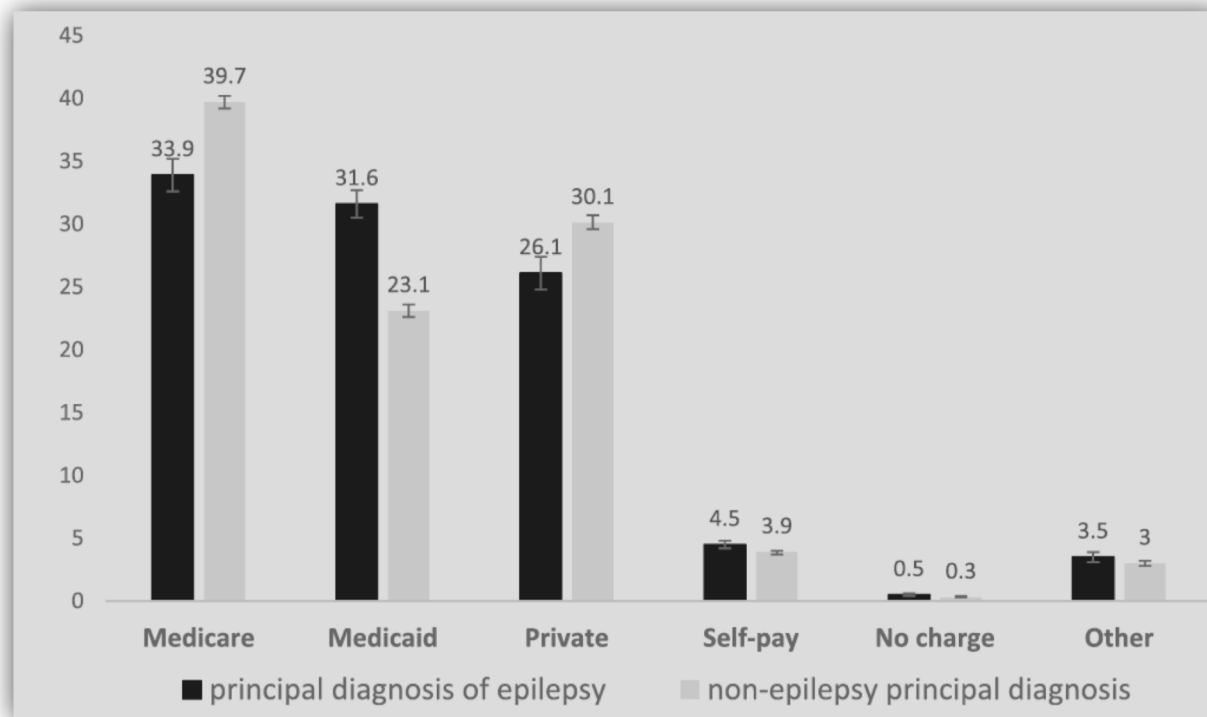
Geographic
difference in
pediatric
neurologists

Underdiagnosis of
epilepsy in some
regions

Unavailability of
genetic tests

Insufficient
treatment in rural
areas
Treatment gaps

Medical care and epilepsy in USA



- Medicaid and Medicare paid about 65% of all inpatient hospitalization costs for all-age persons hospitalized with epilepsy as the principal diagnosis.
- Hospital and admission characteristics, and geographic region differed between hospitalizations with epilepsy versus those with a nonepilepsy discharge.

Medical care and epilepsy in USA

- Most epilepsy discharges occur among those with lower median income levels.
- Most discharges occurred among urban teaching hospitals, followed by urban non-teaching hospitals, and rural hospitals.
- The proportion of hospital discharges from urban teaching hospitals was significantly higher among epilepsy discharges (77.0%) than among nonepilepsy discharges.
- The higher proportions of disadvantaged individuals with increased disease burden in urban areas.
- The large concentration of community and teaching hospitals in densely populated urban areas in the Northeast.
- Increased use of urban hospitals by rural residents in need of complex care, or people's preference in seeking specialty care in teaching hospitals.

Geographic difference and epilepsy in USA

Most discharges occurred among urban teaching hospitals, followed by urban non-teaching hospitals, and rural hospitals.

The proportion of hospital discharges from urban teaching hospitals was significantly higher among epilepsy discharges (77.0%) than among nonepilepsy discharges (65.3%).

Most epilepsy discharges occur among those with lower median income levels.

People's preference in seeking specialty care in teaching hospitals.

Geographic difference in seeking care in epilepsy.

Treatment gaps in epilepsy in children

Magnitude of the epilepsy treatment gap by region and location

Continent/Location	No of studies	TG%	L 95% CI	U 95% CI
Latin America	7	55.4	39.0	78.6
Asia	4	64.3	24.3	100.0
Africa	3	48.9	14.3	100.0
Urban	7	46.8	34.1	64.2
Rural	7	73.3	49.5	100.0

Cause of the epilepsy treatment gap expressed as median and range

Causes of ETG	No of studies	Median (%)	Minimum (%)	Maximum (%)
Cost of treatment	8	62	11	90
Superstitions and cultural beliefs	5	40	7	65
Unavailability of drugs	5	53	18	44
Long distance to health facilities	3	18.5	18	19
Traditional treatment	3	44	6	82
Inadequate skilled manpower	3	70	64	76

Several studies have reported that over 90% of people with epilepsy in developing countries do not receive appropriate treatment for their condition, a phenomenon known as the treatment gap (TG)

Epilepsy in Asia: Disease burden, management barriers, and challenges

TABLE 6 Treatment gap in Asia by country^{a86-96}

Country	Treatment Gap, %
China	
Tibet Autonomous Region	97
Hunan	93.4
Guangxi	79.1
Sichuan	66.3
5 provinces ^b	62.6 ^c
India	73.7-78
Jharkhand	95
Laos	90
Pakistan	88
Vietnam	84.7
Nepal	>70
Philippines	50-77
Cambodia	65.8
Singapore	6

^aCountries for which information is available.

^bHeilongjiang, Ningxia, Henan, Shanxi, and Jiangsu.

^cReduced to 49.8% after community-level interventions.

TABLE 1 Prevalence and incidence of epilepsy in Asia^{3,6,13-27}

Country	Prevalence	Incidence
Vietnam	4.4-14.0/1000	
India	3.0-11.9/1000	38.0-60.0/100 000
Rural areas	5.5-11.9/1000	
Urban areas	5.1-5.8/1000	
Pakistan	10.0/1000	
Laos	7.7/1000	
Nepal	7.3/1000	
Thailand	7.2/1000	
Cambodia	5.8/1000	
China	4.6-7.0/1000	28.8-35.0/100 000
Singapore	3.5-5.0/1000	
Japan	2.7-40/1000	24-53/100 000
Taiwan	2.4-5.85/1000	97/100 000
Korea	2.28/1000	
Hong Kong	1.5-3.94/1000	

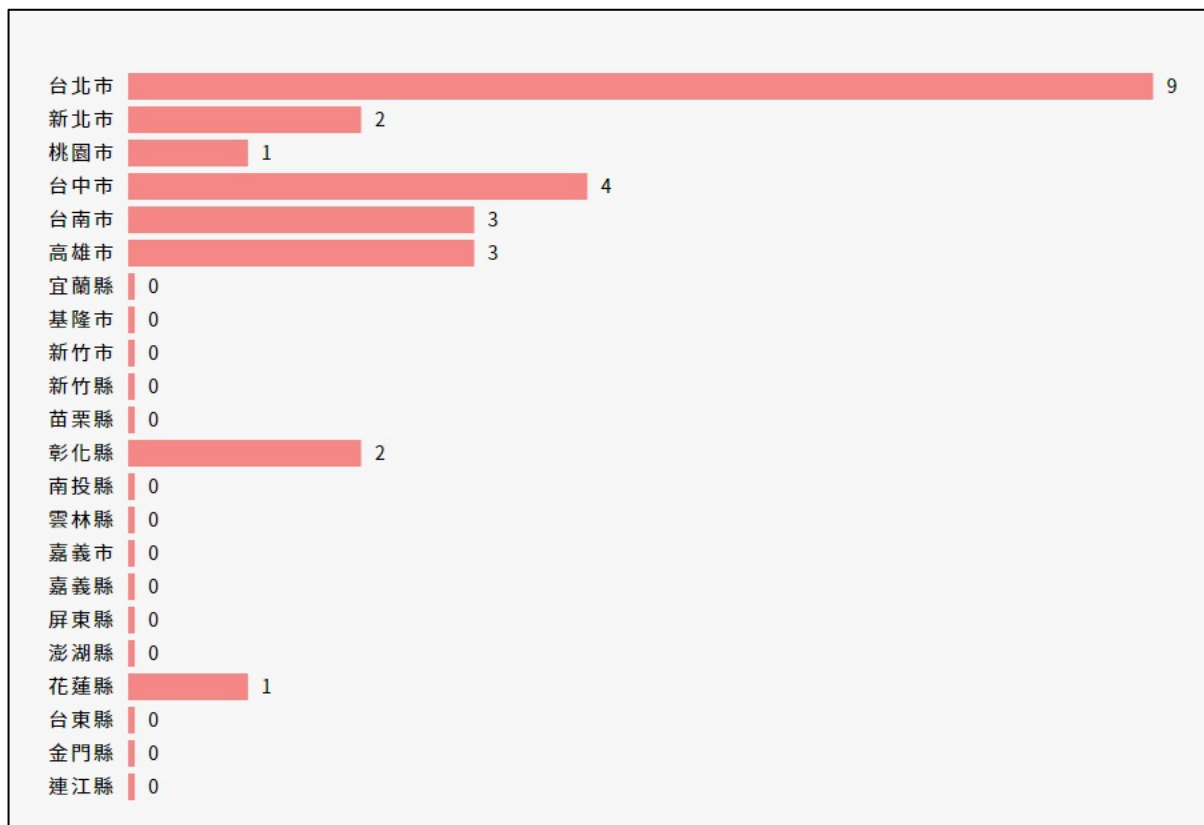
Treatment gap in epilepsy

The prevalence of epilepsy is higher in developing countries.

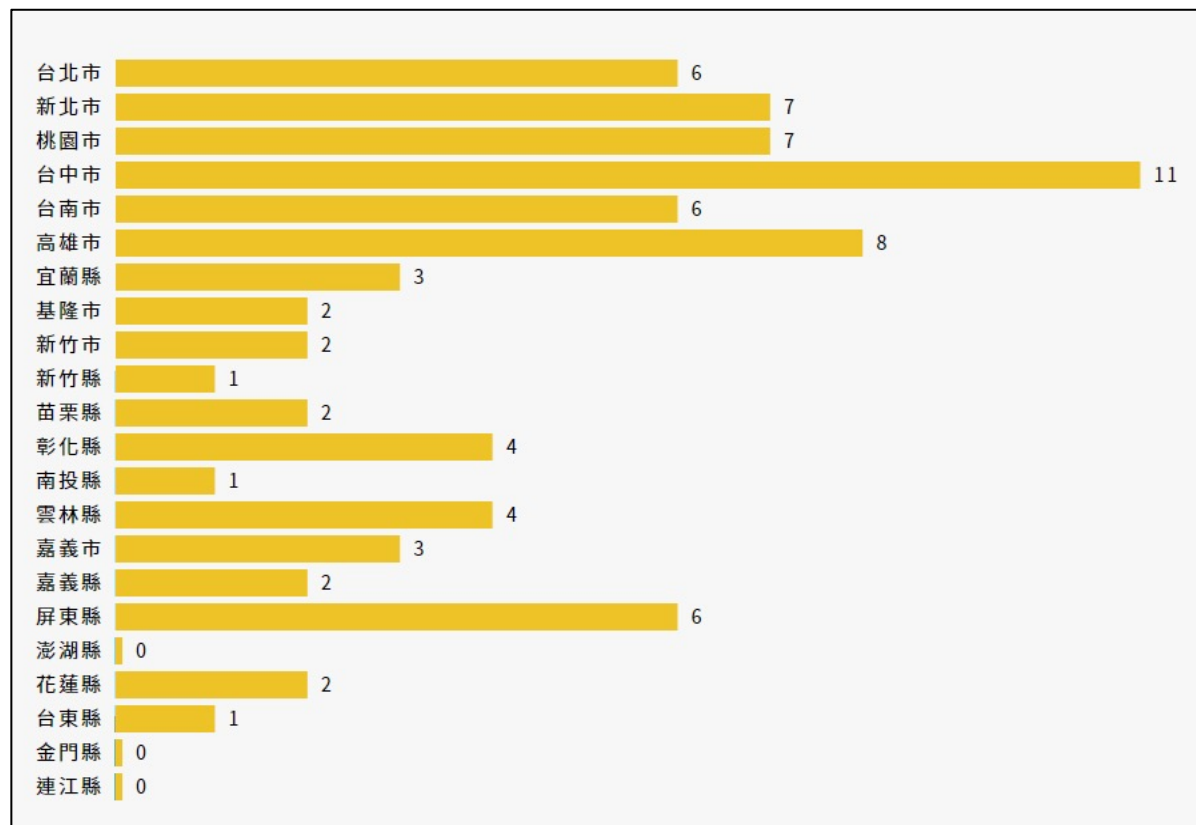
Variation of geographic difference in the prevalence and incidence of epilepsy.

Treatment gap is greater in developing countries.

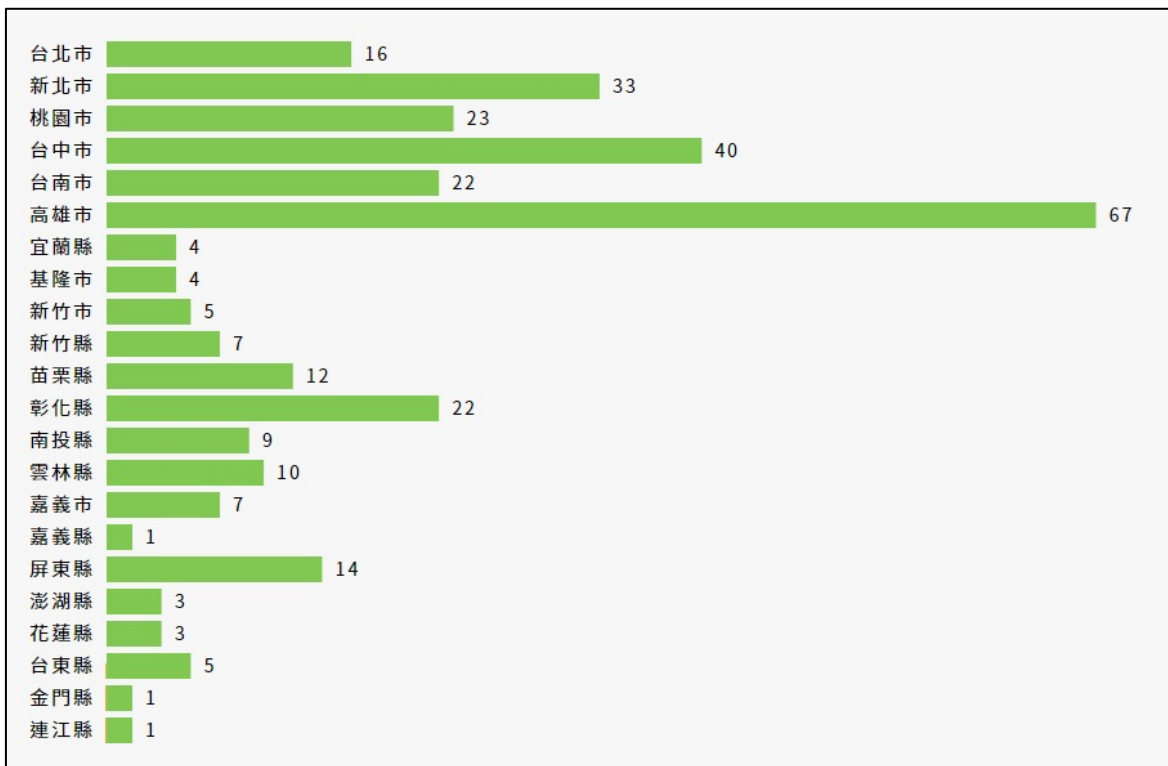
Inadequate skilled manpower, cost of treatment, cultural beliefs and unavailability of anti-epileptic drugs (AEDs).



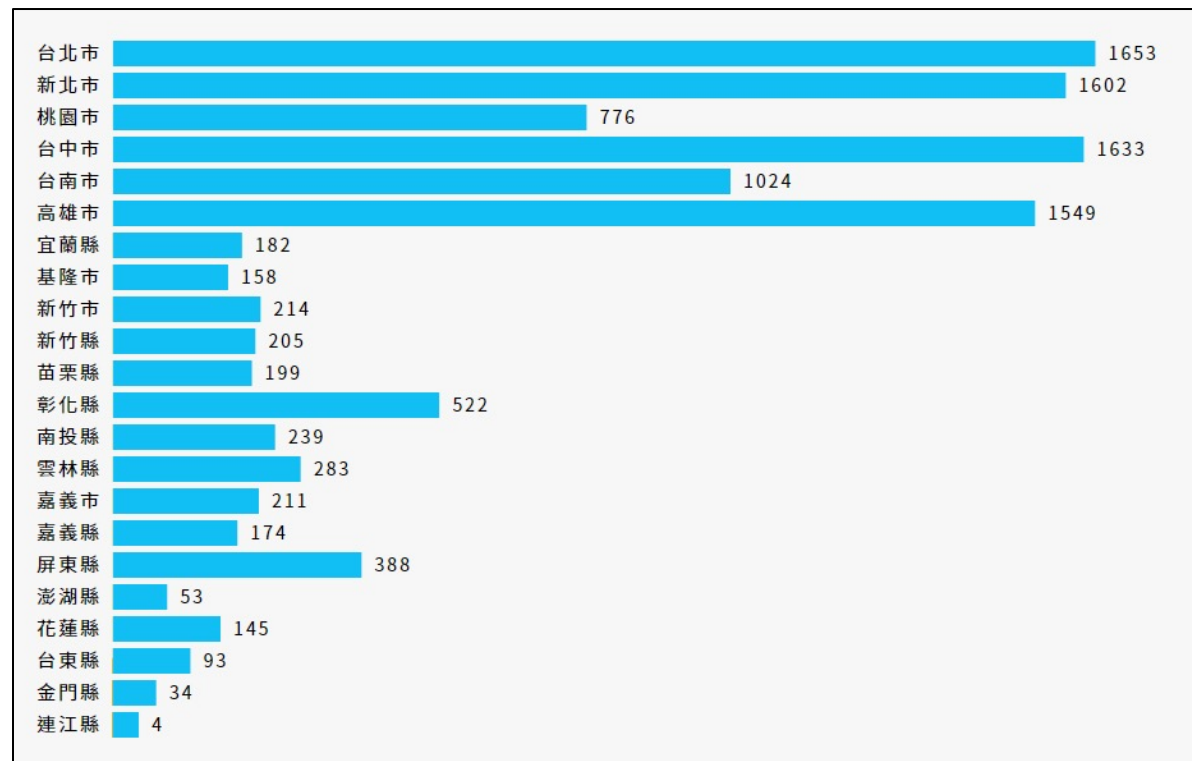
醫學中心



區域醫院

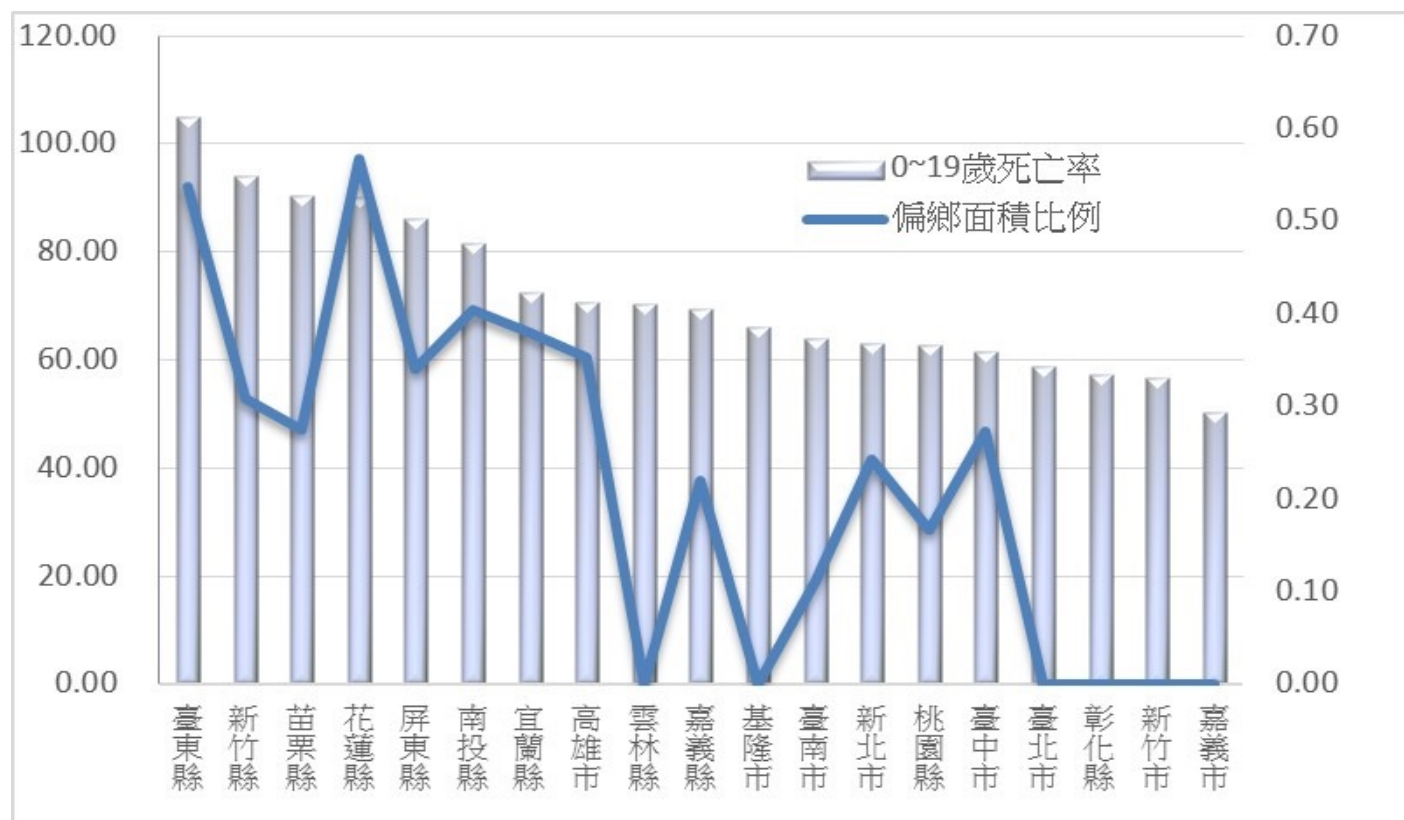


地區醫院



診所

台灣各地區兒童死亡率與偏遠地區面積比例



引自陳篩遐,2016

Geographic variation in Taiwan

In East Taiwan, the rift valley presents a unique geographic landscape not seen in other areas.

East Taiwan also has the lowest economic development status and is home to a mixture of racial populations.

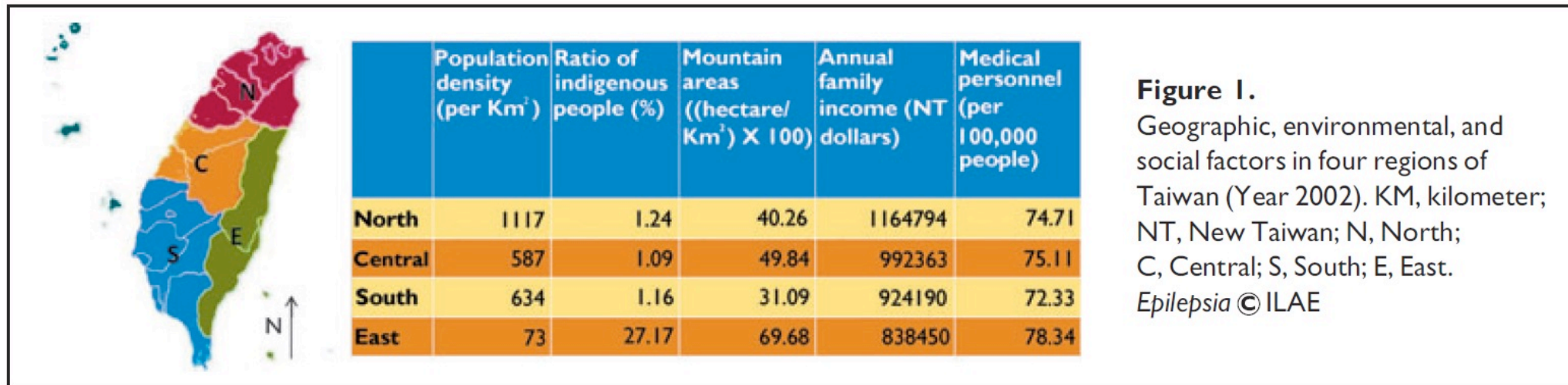


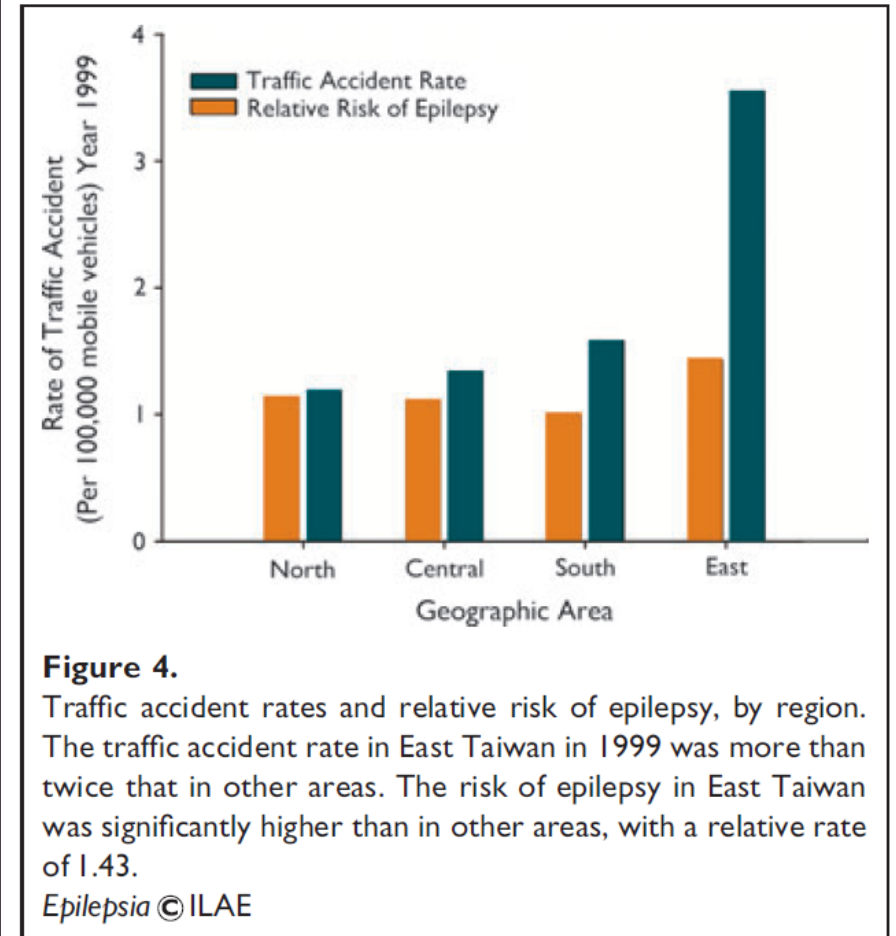
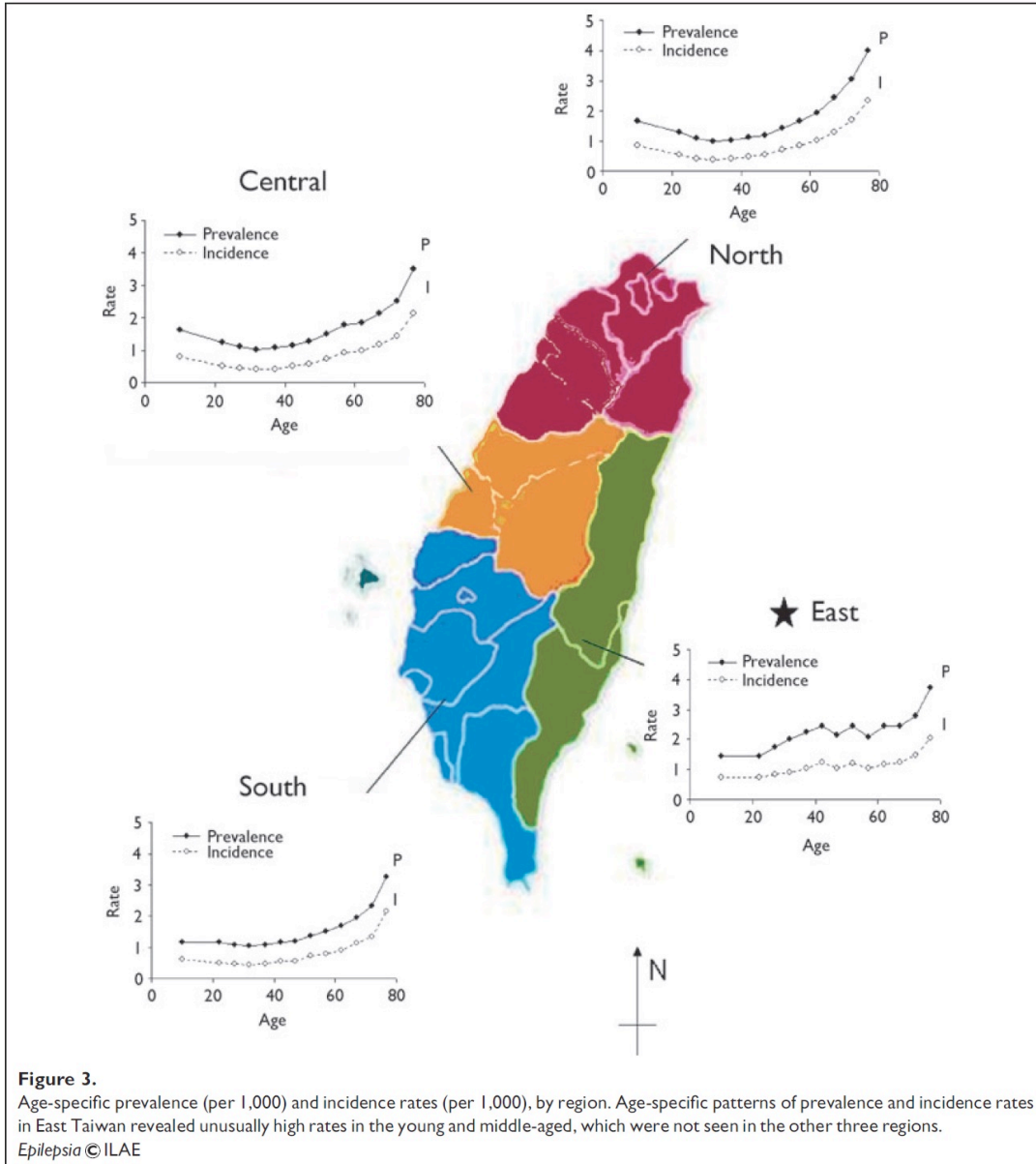
Table 1. Gender- and age-specific prevalence and incidence (per 100,000) of epilepsy during the period 2001–2003 in Taiwan

	Period prevalence (2000–2003) Number of cases (%)	New cases	Person years (2001–2003)	Incidence rate
Sex				
Female	54,305 (4.94)	26,794	32,542,737	82
Male	76,982 (6.72)	37,943	34,018,488	112
Total	131,287 (5.85)	64,737	66,561,225	97
Age group (years)				
0–19	37,947 (5.97)	19,579	19,650,687	100
20–24	9,989 (5.01)	4,271	5,984,581	71
25–29	8,132 (4.42)	3,312	5,319,278	62
30–34	7,698 (4.16)	3,052	5,624,240	54
35–39	8,352 (4.34)	3,502	5,826,891	60
40–44	8,813 (4.69)	3,968	5,502,359	72
45–49	8,378 (4.95)	3,856	4,916,729	78
50–54	7,510 (5.81)	3,783	3,275,417	115
55–59	5,452 (6.6)	2,811	2,443,168	115
60–64	5,866 (7.41)	3,130	2,294,430	136
65–69	5,854 (8.81)	3,243	1,965,952	165
70–74	6,329 (10.74)	3,553	1,735,993	205
75+	10,967 (14.63)	6,677	2,021,500	330
Total	131,287 (5.85)	64,737	66,561,225	97

Table 2. Risk of epilepsy from the multivariable Poisson regression model

Variable	Relative rate	95% CI		p-value
		Lower	Upper	
Area				
South	1.00			
North	1.13	0.94	1.32	0.1466
Central	1.11	0.91	1.31	0.2334
East	1.43	1.10	1.77	0.0043
Age (years)				
20–24	1.00			
<20	1.43	1.38	1.48	<0.0001
25–29	0.84	0.80	0.88	<0.0001
30–34	0.77	0.73	0.81	<0.0001
35–39	0.85	0.81	0.89	<0.0001
40–44	0.99	0.94	1.03	0.6455
45–49	1.07	1.02	1.12	0.0061
50–54	1.38	1.31	1.44	<0.0001
55–59	1.59	1.51	1.67	<0.0001
60–64	1.85	1.76	1.94	<0.0001
65–69	2.28	2.17	2.39	<0.0001
70–74	2.77	2.64	2.90	<0.0001
75+	4.11	3.95	4.28	<0.0001
Gender (male vs. female)	1.35	1.33	1.37	<0.0001
SES (average annual family income)	0.87	0.54	1.20	0.4482

East Taiwan had a statistically significant higher risk of epilepsy after adjustment for age, gender, and social economic status (SES). Low SES showed a nonsignificant trend toward higher incidence.



Age- and sex-specific prevalence of epileptic seizures and epilepsy in Taiwan

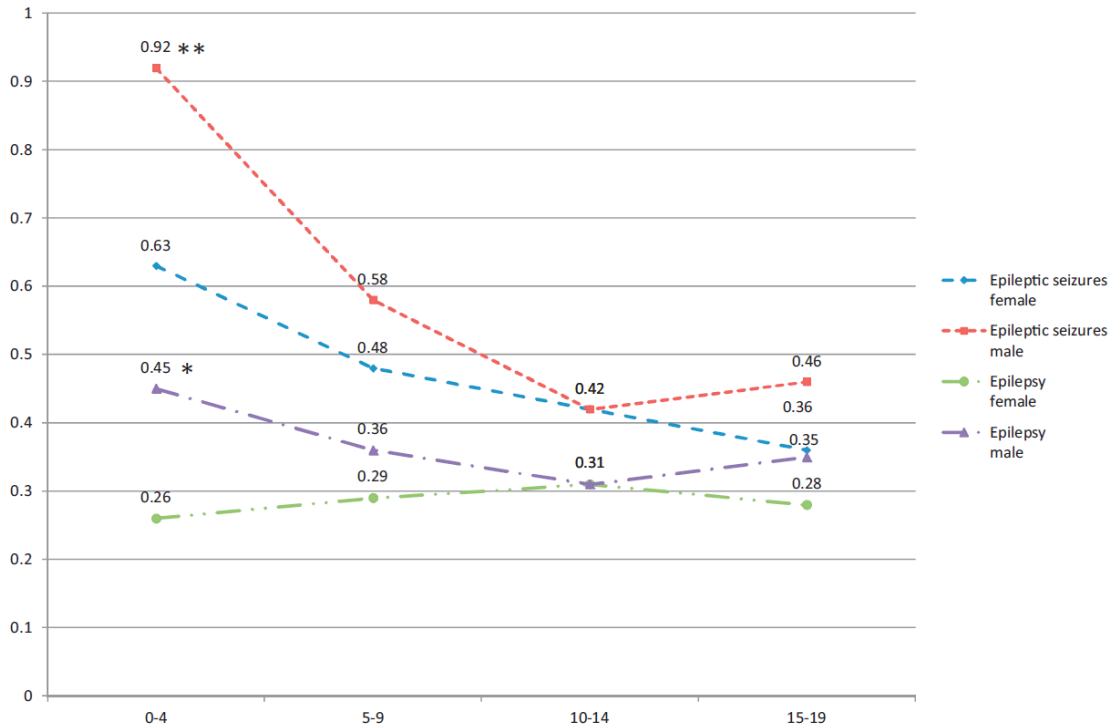


Figure 2 Prevalence of epileptic seizures and epilepsy in the function of age and sex categories in 2005 in our study. ** $p < 0.01$ (epileptic seizure: male vs female in 0–4 group); * $p < 0.05$ (epilepsy: male vs female in 0–4 group).

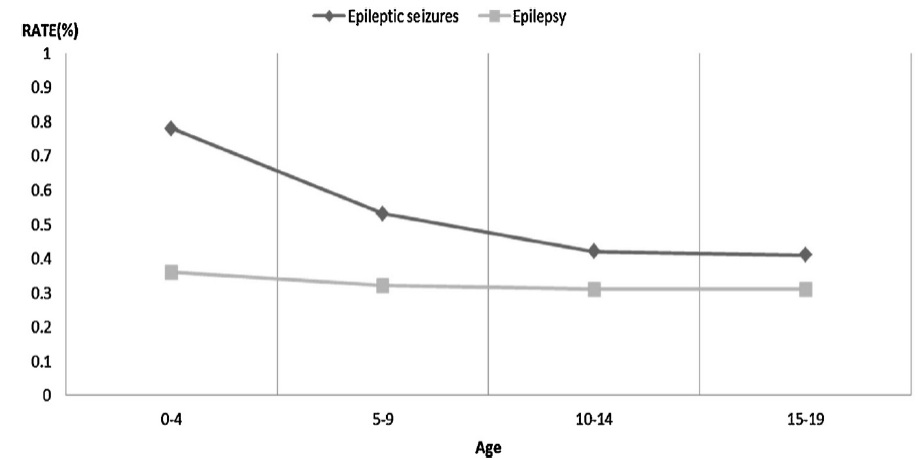


Figure 1 Age-specific prevalence rate in current study.

Influence of urbanization on pediatric epilepsy and the comorbidities in Taiwan

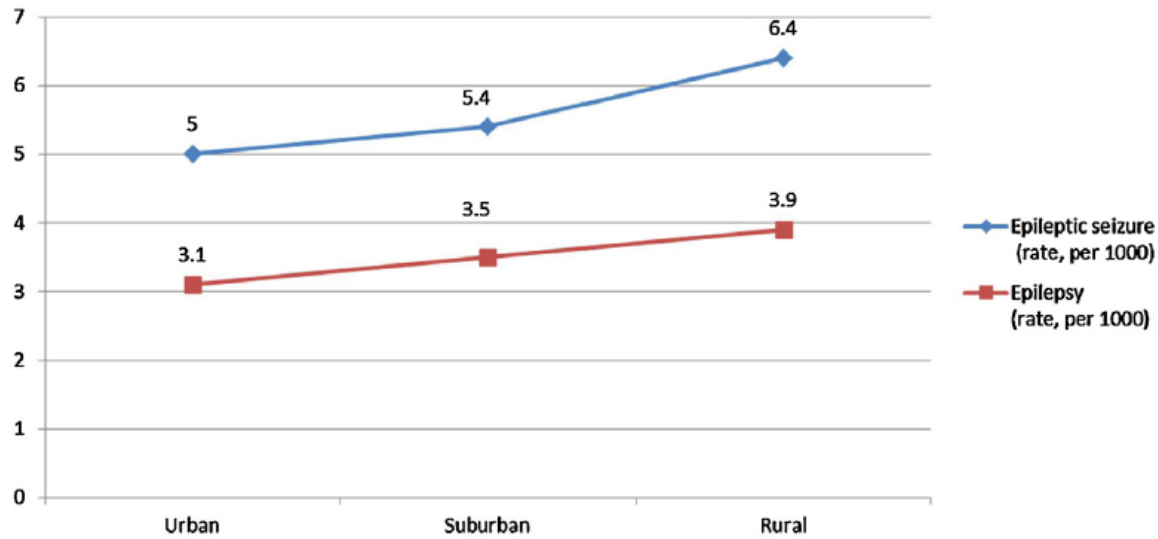


Figure 3 Prevalence rate of epilepsy and epileptic seizure divided in urbanization level.

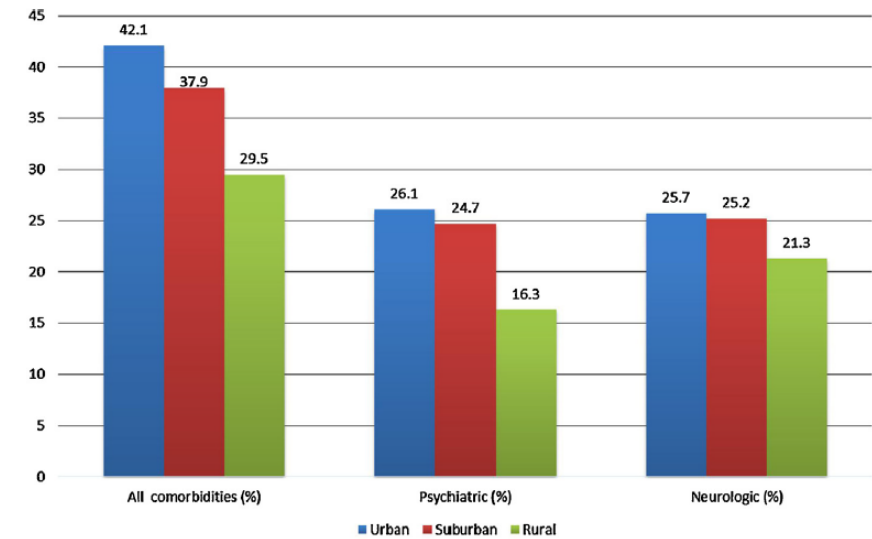


Figure 4 Comorbidity rate of epileptic seizure with urban stratification.

Pediatric neurologists and psychiatrists in Taiwan

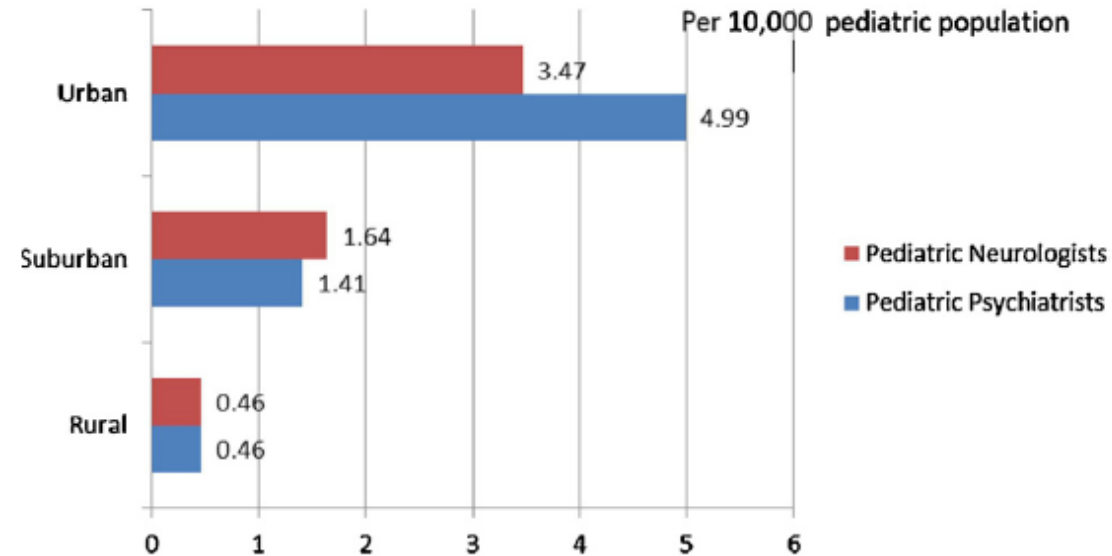


Figure 5 *Lasted available density of pediatric neurologists and psychiatrists (total number per 100,000 population by urbanization stratification, age below 20 years old). *Reference: (1) Official website of Taiwan Child Neurology Society. (2) Official website of Taiwanese Society of Child and Adolescent Psychiatry. (3) Population data from National health insurance research database 2011.

Our study : Inclusion flow chart -- Incidence

Original claims data from NHIRD during 1998-2014
Inclusion criteria : age \leq 19y, ICD9: 345.XX
n = 164,032



Exclusion :
Diagnosed before the end of 2000 (n = 61713)

Age \leq 19y, ICD9: 345.XX during 2001-2014
n = 102,319



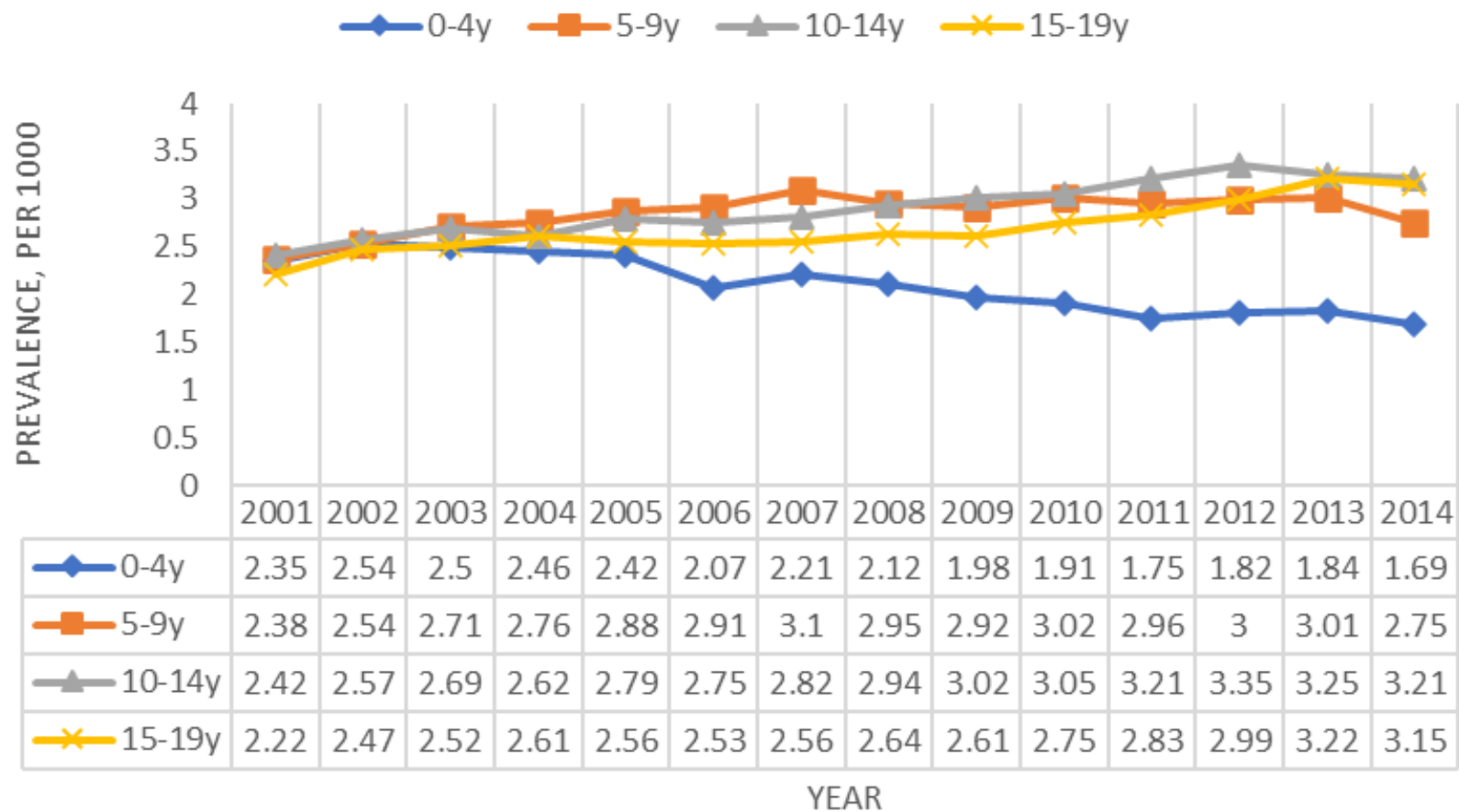
Exclusion :
1) No AEDs use (n = 61264)
2) The total visiting clinic or admission $<$ 3 times during 2001-2014

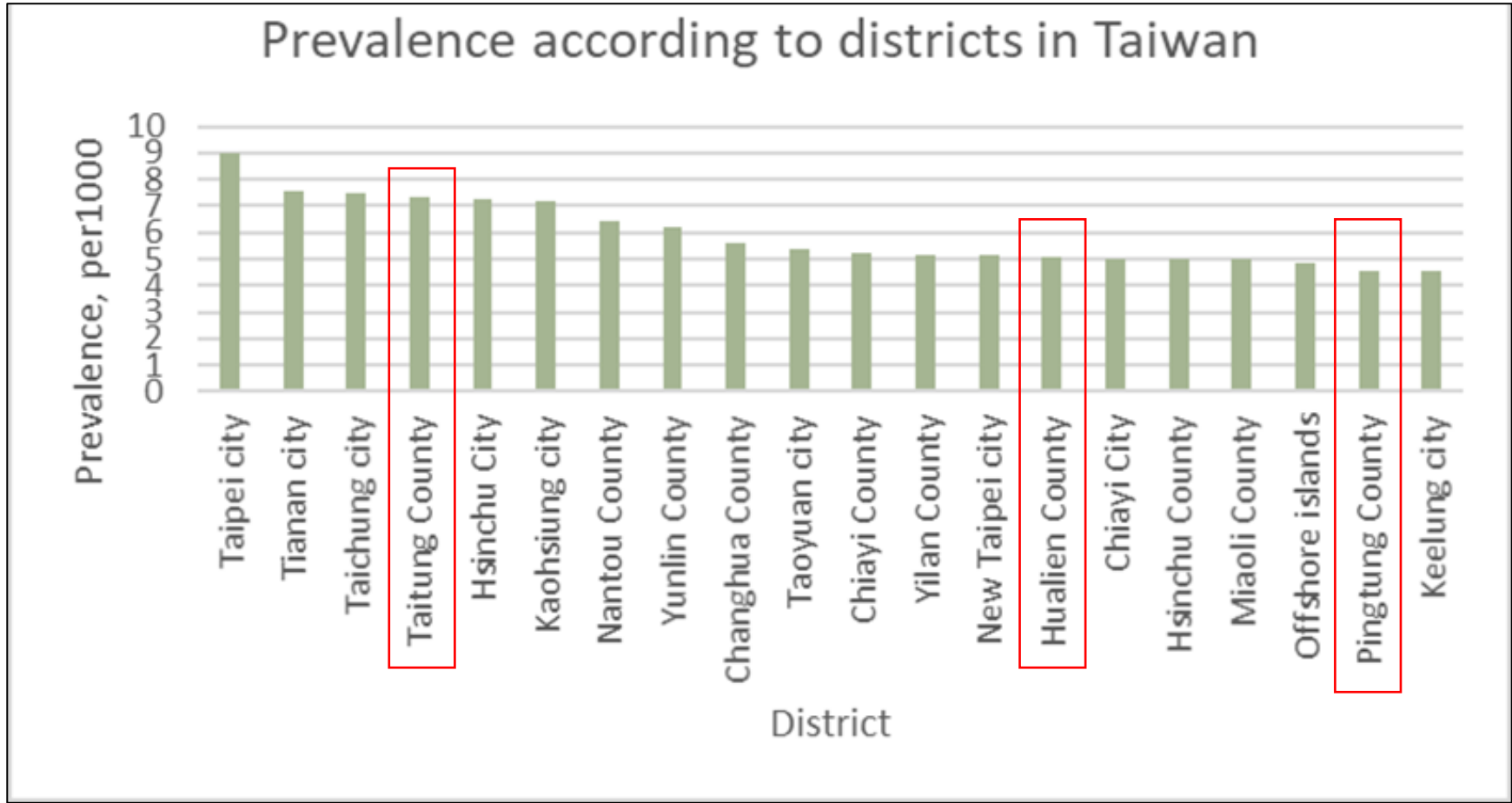
Subjects for analysis
n = 30,666

Result -- Comparison

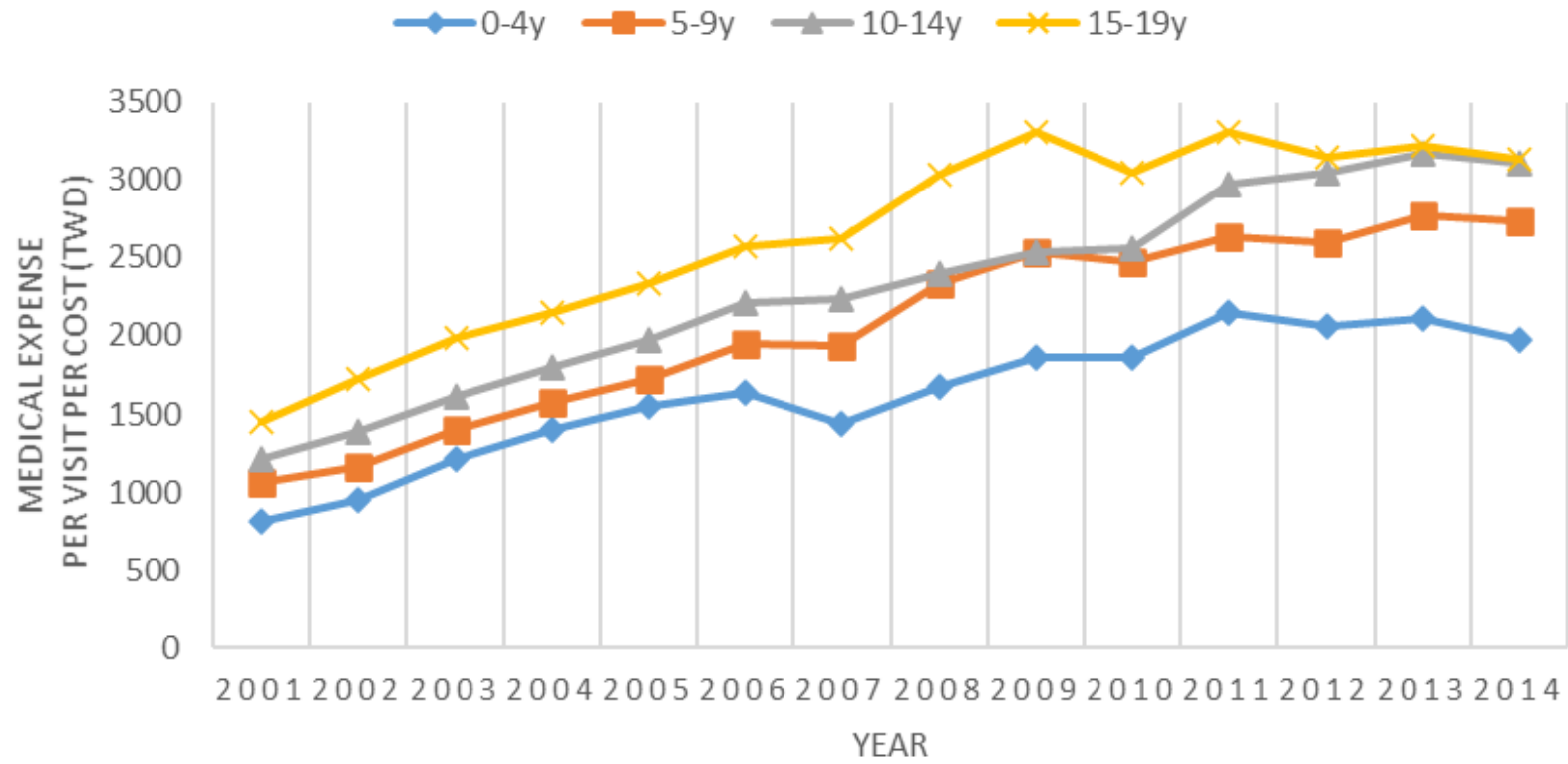
	USA	Canada	Latin America	Europe	Kenya 6-9y/o	India	Japan	Hong-Kong	Our study
Prevalence per 1000	6.8	5.26	7.5-44.3	4.2-5	11	6.24	5.3	4.3	2.3-2.9
Incidence per 100,000	104	41	--	70	187	--	70.4	--	24-44

PREVALENCE

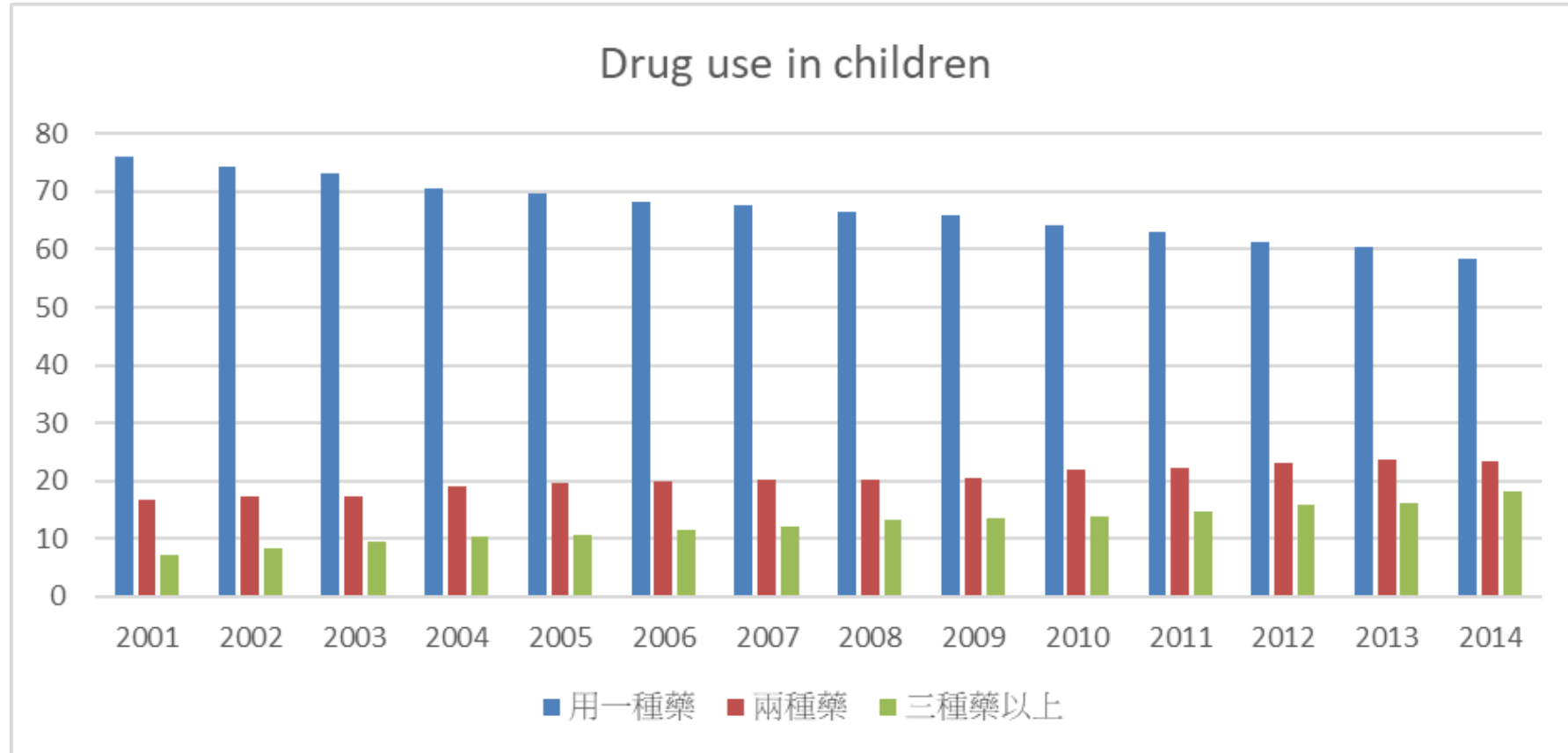




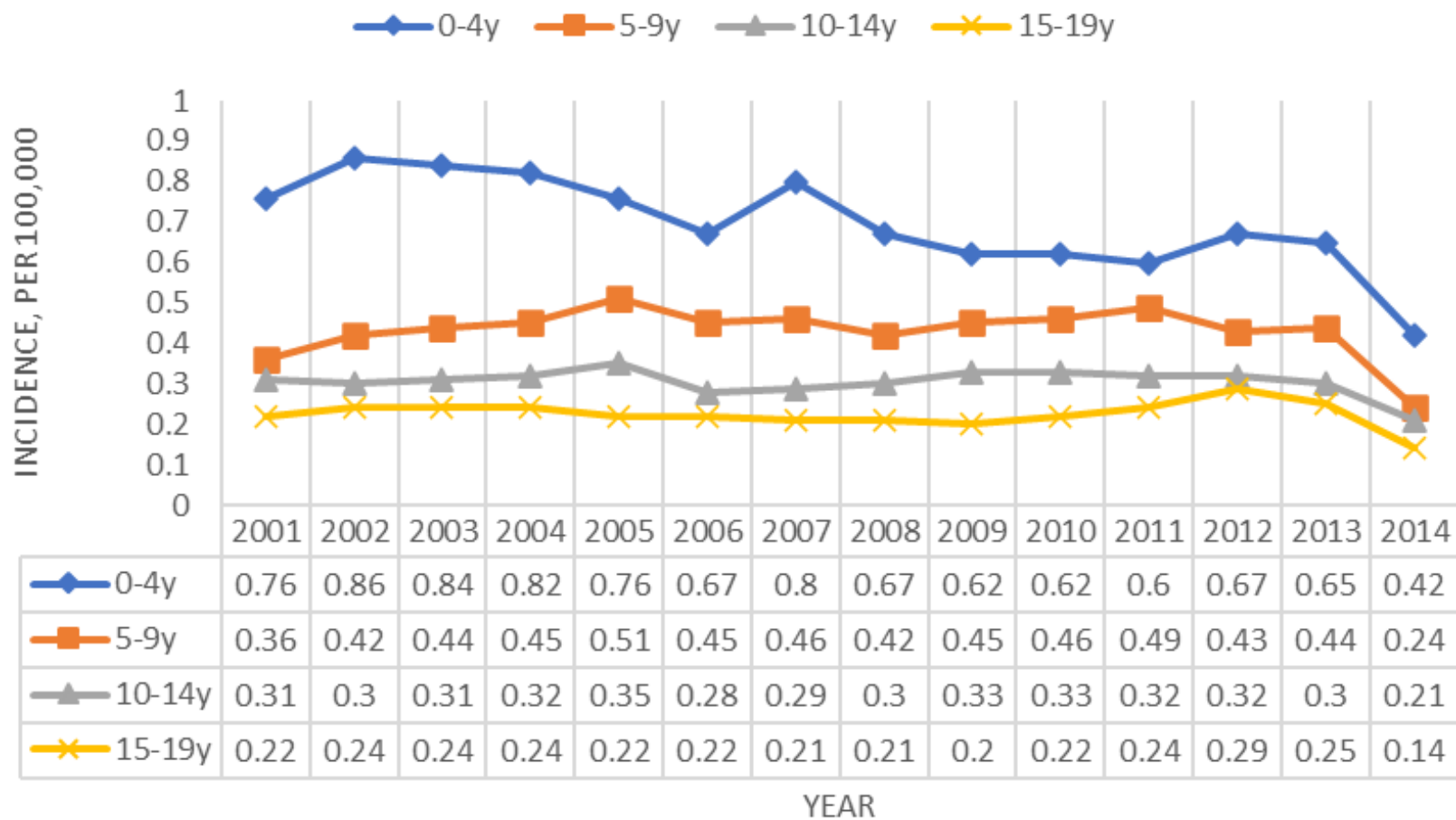
MEDICAL EXPENSE PER CLINIC VISIT



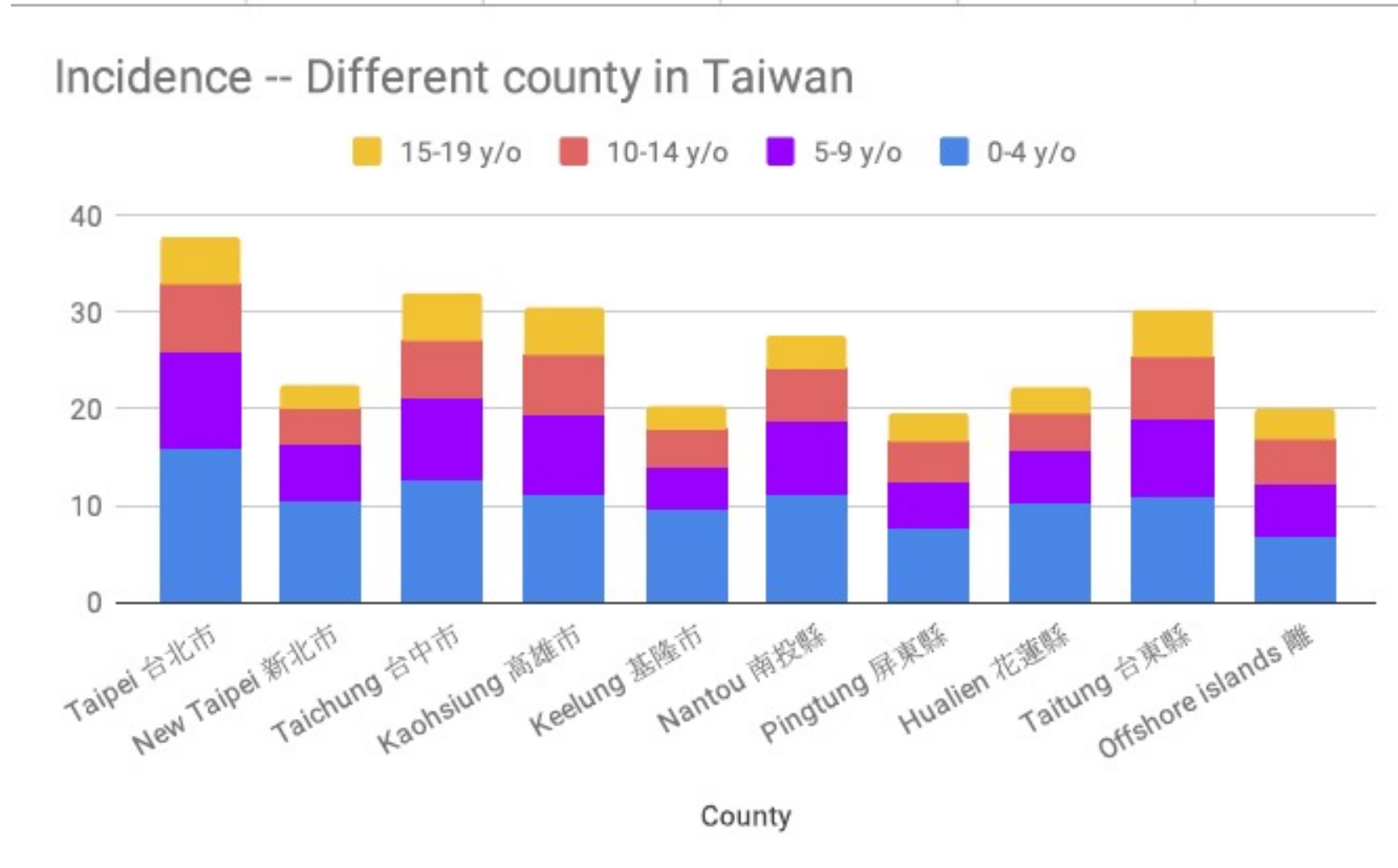
Antiepileptic drug use in Taiwan



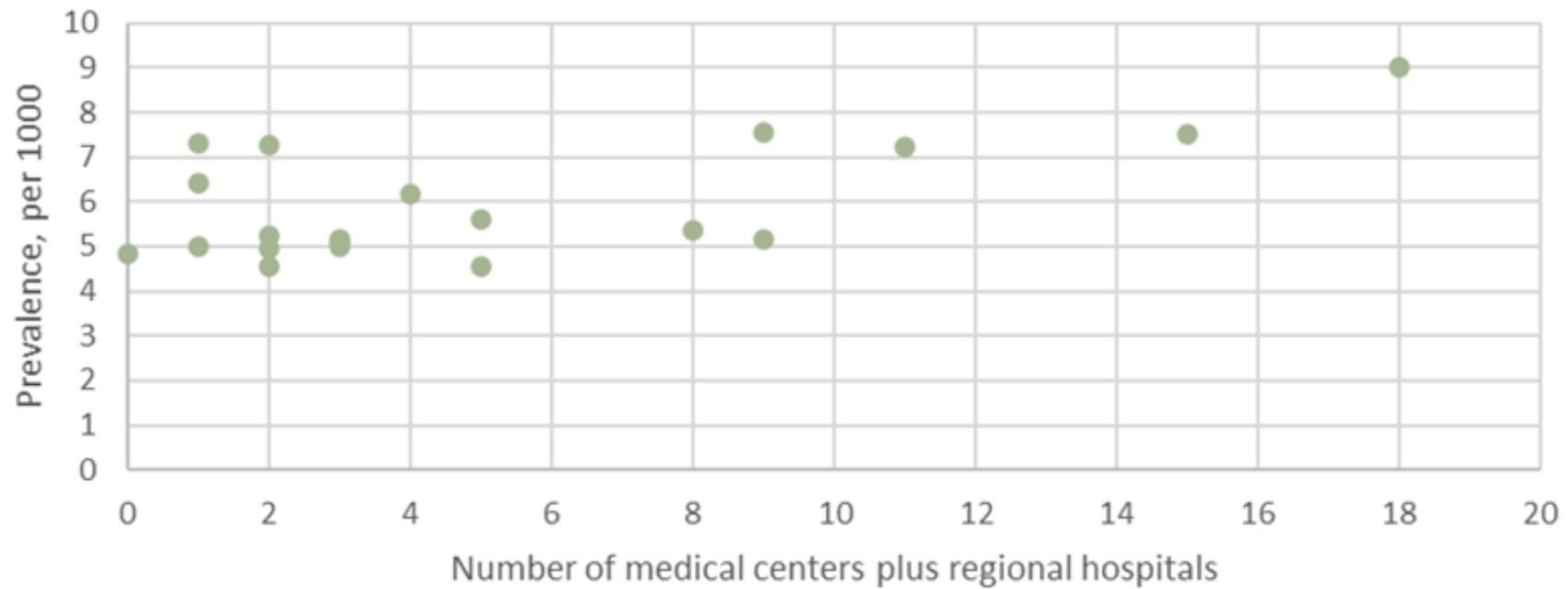
INCIDENCE



Geographic variation



Correlation between Prevalence and Total number of medical centers and regional hospitals



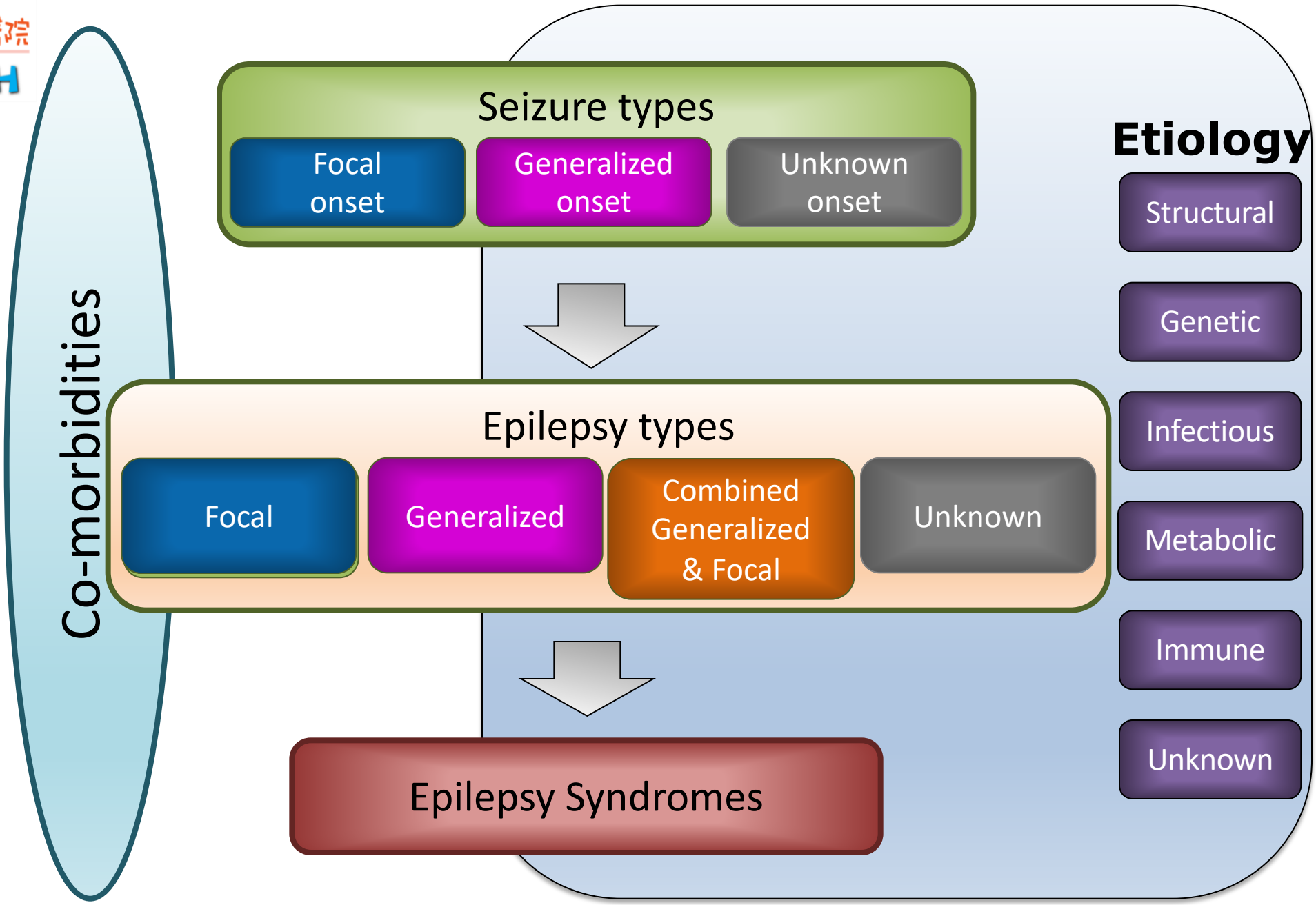
Epilepsy of children in Taiwan

The prevalence and incidence of epilepsy in young children are decreasing.

The prevalence and incidence of epilepsy in children are not higher compared with other countries.

The prevalence and incidence of epilepsy in rural areas are not lower than urban areas.

The hospital number and pediatric neurologist number are much lower in rural areas.



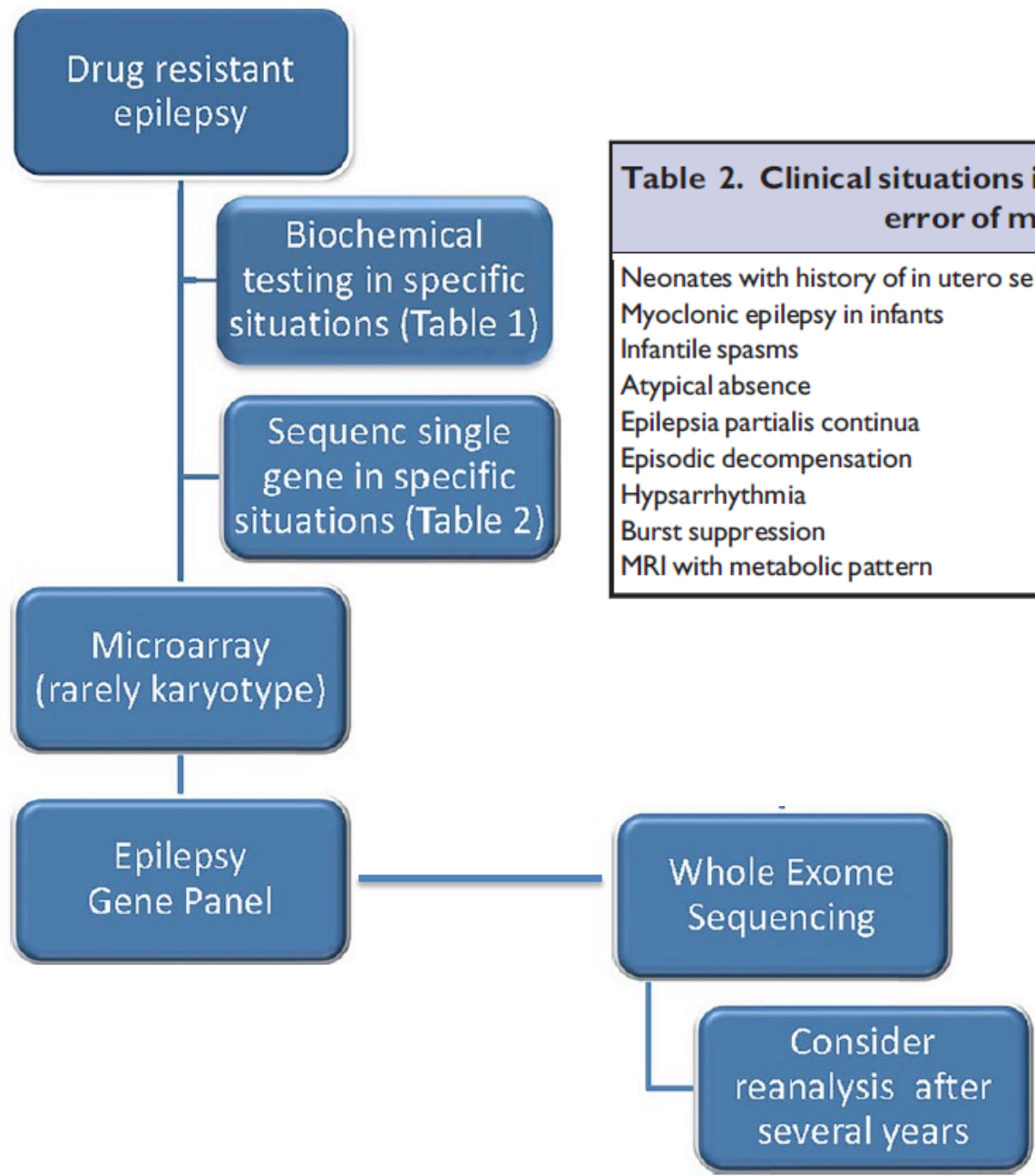


Table 2. Clinical situations in which to suspect an inborn error of metabolism.

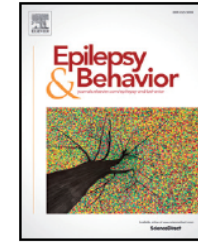
- Neonates with history of in utero seizures
- Myoclonic epilepsy in infants
- Infantile spasms
- Atypical absence
- Epilepsia partialis continua
- Episodic decompensation
- Hypsarrhythmia
- Burst suppression
- MRI with metabolic pattern



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The role of targeted gene panel in pediatric drug-resistant epilepsy



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ABSTRACT

About 10–30% of pediatric patients with epilepsy have drug-resistant epilepsy. Genetic panels may be useful in identifying etiology and guiding treatment in pediatric patients with drug-resistant epilepsy. In our tertiary center, we used two epilepsy panels, an initial 24-genes panel followed by a more comprehensive 122-genes panel to screen for genetic cause over recent 2 years. A total of 96 patients with drug-resistant epilepsy were evaluated using the 24-genes panel, which revealed 10 (10.4%) of the patients with pathogenic variants. Another 22 patients without causative genetic variants using first-gene panel were evaluated using the 122-genes panel. Out of the 22 patients, 4 had pathogenic variants, and 6 had variants of unknown significance. The total yield rate for the second panel was 18.2% (4/22). In conclusion, although whole exome sequencing has entered clinical practice, epilepsy gene panels may still play some roles because of lower cost and faster time, especially in those with fever-associated epilepsy.

兒童醫學及健康研究中心(國衛院)

- 工作劃歸國衛院底下
- 不是醫療單位，角色功能僅限於政策研究。
- 曾推動重難症計劃三年，但後續就沒有經費推動



Our Epilepsy Gene Panel

30 genes

*ALDH7A1, ALG13, ARX,
CACNB4, CDKL5, CHD2,
DEPDC5, DNM1,
GABRA1, GABRB3,
GABRG2, GNAO1,
GRIN1, GRIN2A, KCNA2,
KCNQ2, KCNT1, PCDH19,
PIGA, PLPBP, PNKD,
PNPO, PRRT2, SCN1A,
SCN2A, SCN8A, SLC2A1,
SMC1A, STXBP1,
TBC1D24*



**Specific or molecular-targeted
therapy for EEs**

Specific or molecular-targeted therapy for EEs

Gene	Epilepsy/Phenotypes	Treatment
<u>ARX</u>	XLAG, Ohtahara syn., West syn., etc.	Vigabatrin
<u>GNAO1</u>	Ohtahara syn., etc.	Gabapentin
<u>GRIN2A</u>	EOEE	Memantine
<u>KCNT1</u>	Migrating partial seizures in infancy	Quinidine
<u>KCNQ2</u>	Ohtahara syn., etc.	Ezogabine
Ring chromosome 20	Epileptic encephalopathies	Ezogabine
<u>SCN1A</u>	Dravet syn., etc.	Striripentol
<u>SCN2A</u>	EOEE	Lidocaine
<u>SCN8A</u>	EOEE	Phenytoin
<u>SLC2A1</u>	GLUT1 deficiency	Ketogenic diet
<u>STXBP1</u>	Ohtahara syn., etc.	Levetiracetam
<i>TSC2/1</i>	West syn. in TSC	Vigabatrin
<i>TSC2/1</i>	Tuberous sclerosis (TSC)	Everolimus

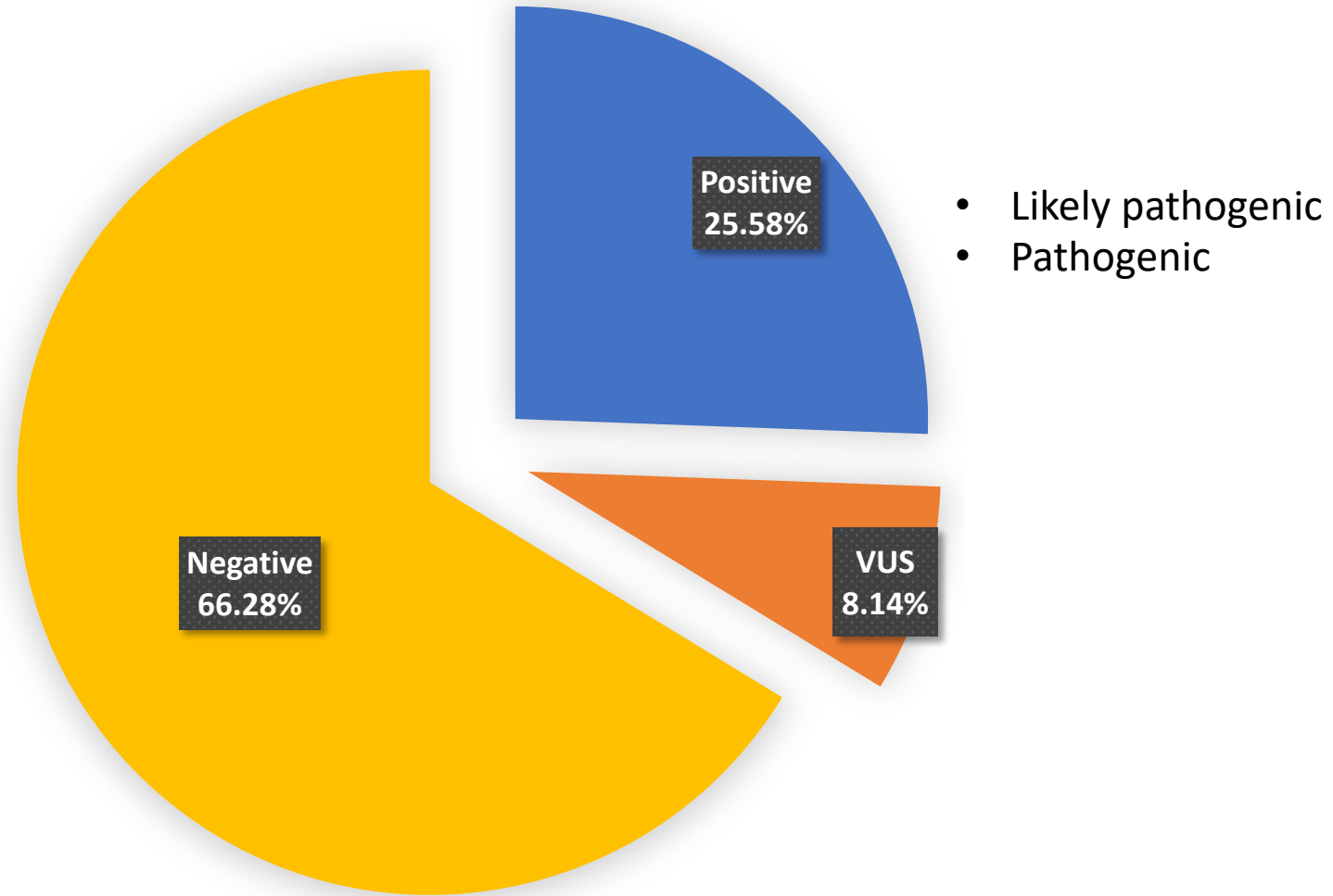
Current progress-demographic data

- Since July 2019 – May2021 (2y)

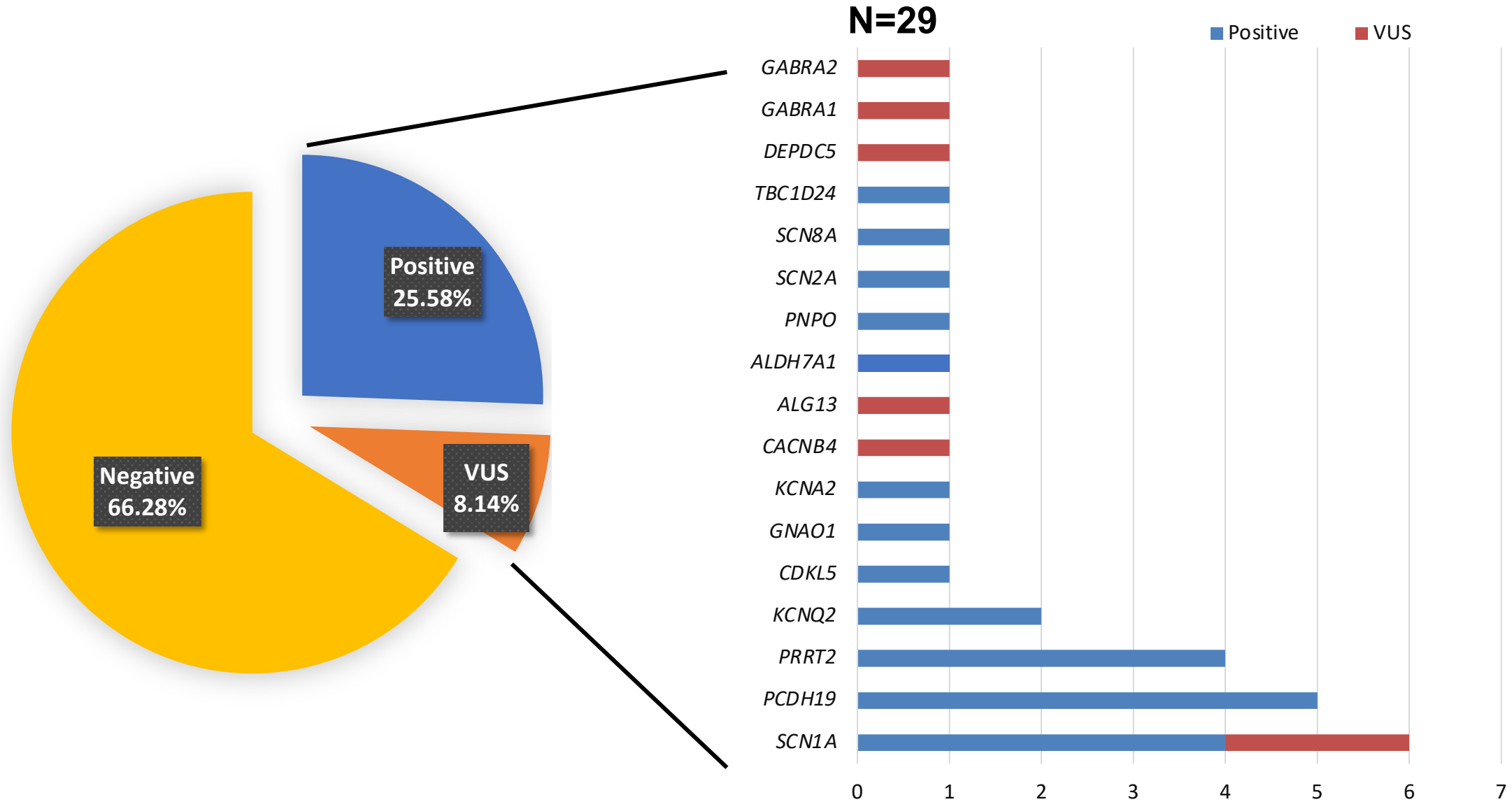
Clinical Features	n=86
Sex (female/male)	35/51
Age, mean(years)	5.11±5.22 (0 days old-21.69 years)
Age of seizure onset(years)	1.71±2.83 (1days-13 years)
Febrile convulsion	19(22.09%)
Movement disorder	6 (6.97%)
Epilepsy	
Generalized	55 (63.95%)
Focal epilepsy	52 (60.47%)
Epileptic spasms	7 (8.14%)

Current progress-diagnostic yield

N=86



Current progress-diagnostic yield



Geographic difference in genetic testing

- Most blood samples come from western part of Taiwan.
- Only one sample comes from eastern part of Taiwan.
- Inadequate diagnosis
- Economic problem

TABLE 7 Epilepsy surgery in Asia by country¹¹⁷⁻¹²⁹

Country	Number of Epilepsy Surgery Centers	Number of Surgeries and Potential Candidates
Hong Kong	3	~150 ~3500 surgical candidates
Japan	43 5 reference centers (performing >25 surgeries/y)	436/y ~2000 surgical candidates
Korea	17	300-400/y
Taiwan	3	>800
Malaysia	1	12
China	5 cities have established epilepsy centers, and at least one hospital in each of the 32 provinces provides epilepsy surgical services	2500/y
India	2	1200
Nepal	1	11
Thailand	3	7 ^a
Indonesia	1	35-47 in 2007-2009
Philippines	4	NA

NA, not available.

^aSince reactivation of the surgical treatment program in 2005.

- Epilepsy surgery is an important therapeutic measure for patients with refractory epilepsy.
- The services are likely to be underutilized given the number of patients who could benefit from epilepsy surgery.
- Changing trends in epilepsy management and newer therapeutic procedures require ongoing training programs.
- There are fewer epilepsy surgery centers in the lower income countries, resulting in a “surgical gap.”

The problems faced in management of epilepsy in children

Unavailable new
treatments in
Taiwan

Geographic
difference in
pediatric
neurologists

Underdiagnosis of
epilepsy in some
regions

Unavailability of
genetic tests

Insufficient
treatment in rural
areas
Treatment gaps

Take home message

- Epilepsy is a common neurological diseases with many comorbidities.
- Prevalence and incidence of epilepsy have decreased in recent years with elevation of medical expanse.
- Variation of geographic difference in the prevalence and incidence of epilepsy.
- Geographic difference in hospital number and pediatric neurologist number.
- Insufficient medical treatment and surgical treatment for children with epilepsy.
- Medical burden is a major issue in some rural areas.



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*Thank you very much for
your attention*