

**Pre-exposure childhood immunization (EPI program):  
Cost effectiveness analysis**

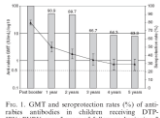
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**Pre-exposure vaccination mainly concerns individuals who are continually or frequently at risk of exposure to rabies**

Rabies Seroprotection rate in children receiving DTP-IPV+PVRV over 5 years of follow-up beginning 2-weeks following administration of the third PVRV dose

	Post-dose 3	1 year	2 years	3 years	4 years	5 years
Anti-rabies titer ≥0.5 IU/ml	36/36	30/33	26/29	20/30	18/28	19/30
n/N, %	100	90.9	89.7	66.7	64.3	63.3



**Rabies vaccine IM 2, 4 mo and 1 year  
DTP-IPV 2, 3, 4 mo and 1 year**

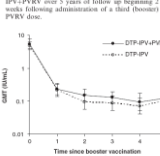
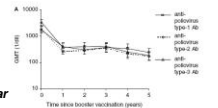


Fig. 2. GMT of anti-rabies antibodies (95% CI) in children given DTP-IPV only or DTP-IPV+PVRV. Five-year follow-up beginning 2 weeks following the fourth (booster) DTP+P dose.



**Lang, Feroldi, Vien. J Trop Ped 2007**

Fig. 3. GMT of anti-poliovirus antibodies (95% CI) in children given DTP-IPV only or DTP-IPV+PVRV. Five-year follow-up beginning 2 weeks following the fourth (booster) DTP+P dose. (A) DTP+P-IPV and (B) DTP+P-IPV+PVRV.

**Randomised feasibility trial of pre-exposure rabies vaccination with DTP-IPV in infants**

Jean Lang, Duong Q Hoa, Nguyen V Giol, Le Tan Tho, Nguyen C Vien, Veronique Kesmejdian, Stanley A Plotkin

Antibody to	Level at which tested	Number positive (%)	
		DTP-IPV (n=43)	DTP-IPV + PVRV (n=41)
Tetanus	0.10 IU/mL	43 (100%)	41 (100%)
Diphtheria	0.01 IU/mL	43 (100%)	41 (100%)
	0.05 IU/mL	43 (100%)	40 (98%)
	0.10 IU/mL	43 (100%)	37 (90%)*
Pertussis	1/40	43 (100%)	41 (100%)
Polio	1/5	43 (100%)	41 (100%)
Rabies	0.50 IU/mL	0	41 (100%)

Rabies vaccine IM 2, 4 mo  
DTP-IPV 2, 3, 4 mo

\*p<0.05; Fisher's exact test.  
Table 1: Seroreversion rates 1 month after last injection

DTP-IPV group	Geometric mean titre (95% CI) in IU/ml		DTP-IPV + PVRV group	
	Baseline	After	Baseline	After
Tetanus	0.17 (0.09-0.31)	1.35 (1.04-1.74)	0.19 (0.09-0.37)	0.93 (0.68-1.27)
Pertussis	14 (9-22)	882 (705-913)	13 (8-21)	838 (655-1098)
Polio virus				
Type 1	42 (26-68)	994 (764-1402)	41 (23-74)	695 (448-1081)
Type 2	174 (105-277)	1165 (835-1628)	144 (80-258)	863 (564-1302)
Type 3	12 (7-20)	1515 (1040-2206)	16 (10-26)	1028 (726-1449)
Diphtheria	0.008 (0.004-0.008)	0.778 (0.575-1.061)	0.011 (0.002-0.017)	0.14 (0.036-0.797)
Rabies	0.000 (0.000-0.000)	0.028 (0.004-0.163)	0.000 (0.000-0.000)	29.09 (15.17-46.48)

Table 2: Geometric mean titres before immunisation (baseline) 1 month after final injection of DTP-IPV (after)

Jean Lang, Duong Q Hoa, Nguyen V Giol, Le Tan Tho, Nguyen C Vien, Veronique Kesmejdian, Stanley A Plotkin. Lancet 1997

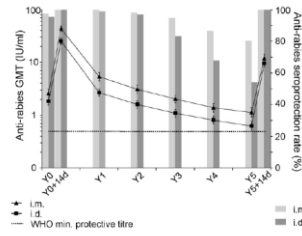


Fig. 1 Anti-rabies antibody titre [geometric mean titre (GMT) and 95% CI, log-scale representation] kinetics and seroprotection (% subjects titre ≥0.5 IU/ml) following pre-exposure purified Vero cell rabies vaccine administered i.m. or i.d.

Nguyen Cong Vien, Emmanuel Feroldi, Jean Lang. Royal Soc Trop Med Hyg. 2008

Primary rabies vaccination series, IM/ID 2 and 4 months.  
At 1 year, IM 113 ID 115  
5 year, IM 86 ID 85

**Pre-exposure childhood immunization (EPI program):  
Cost effectiveness analysis**

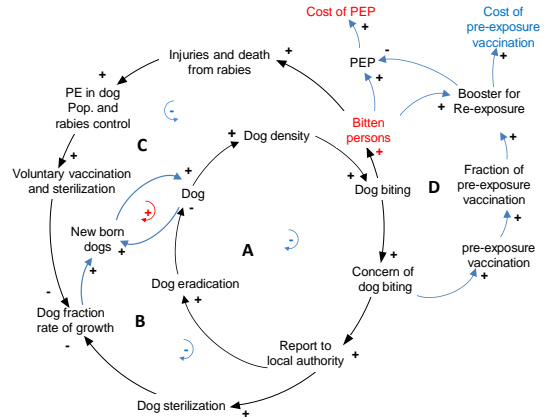
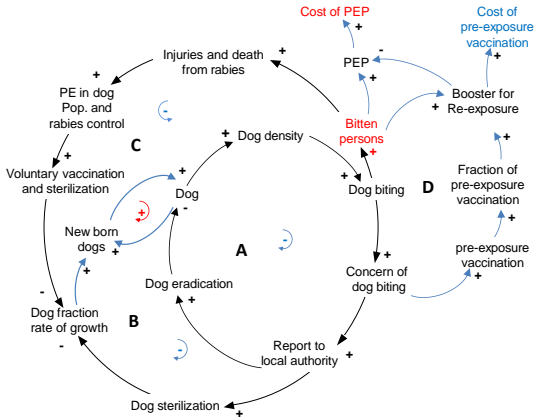
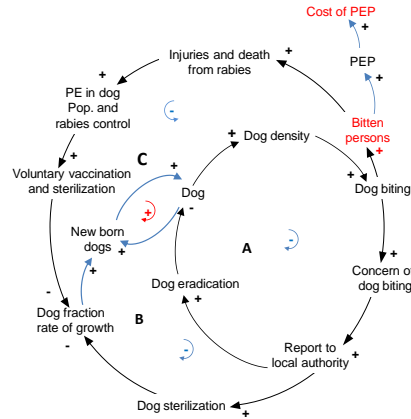
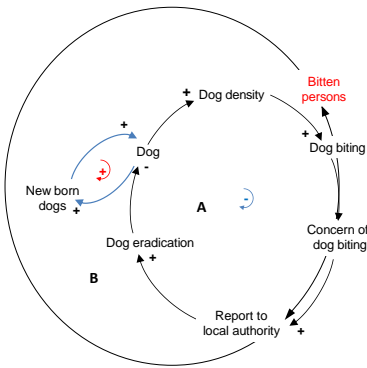
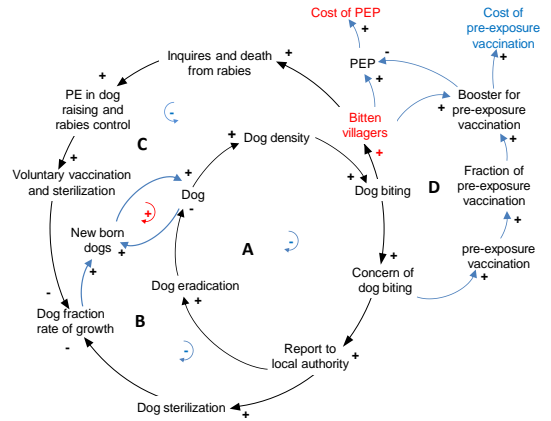
- Using system approach based on factors and variables in rabies
- STELLA program, a simulation system which provides feedback, in projecting a scenario using parameters that are available in Thailand to determine whether it is worth to incorporate rabies vaccine into EPI program in terms of cost effectiveness

**Parameters and variables**

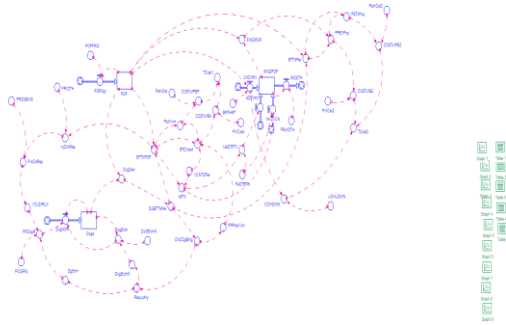
- Dog population is numbered at 1:4 of humans (a family of 4 members). 12 millions dogs were estimated with human population of 64 millions.
- Fraction of dog growth rate. 100 will become 112.5 at the end of one year. Calculation was based on 4 births x 2/year but the number is regulated by death at birth, accident, malnutrition, infection. Retarded by controlled factors from human interventions. Growth rate is not exponential. Male: female = 1
- Rate of dog bites = 500,000/year with 20 deaths
- Severe injuries needed for meticulous care = 3%, 1 year = 15,000 or 1,250/month 1 province in Thailand = 1,250/76 = 16.4/province/month
- Frequency of becoming news (FRQNEWS)=15,000/1,000 (hypothetical no) = 15 news/year/country (varying number 0-60 or average of 15)
- Impact or effect of news leads to increase in voluntary sterilization resulting to decrease dog net growth rate

# Parameters and variables

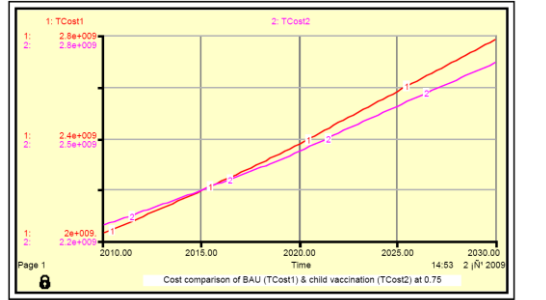
- Concern among community members once heard of dog biting incidence and heard of requirement of PEP which needs 4-5 visits and in some cases ERIG [500,000 (current incidence rate = 0.008) Scale varies from 0-100]
- In this case, concern = 2% (0.02) of community population
- This results to report/complaint to local authorities. This may lead to sterilization/vaccination or eradication or re-location (create problem to neighboring countries). Total net growth rate of dogs may be reduced.
- Concern in community also leads to need for PREP
- 2/100 concerns; and 2/100 seeks PREP
- Of 500,000, 15% already had vaccination, thus, requiring only boosters. Children <14 : adult = 1:1
- Cost includes vaccine, wound care, tetanus toxoid, antibiotics, travel cost (excluding doctor fee and opportunity cost)
- Infant mortality rate = 18.23/1000; birth rate = 13.57/1000 (approx. 1 million) Death rate = 7.17/1000
- Human population and birth/death rate and net growth rate (Fraction rate of growth, FRG) = 0.015 (100 humans will become 101.5 at the end of 1 year)



FLOW DIAGRAM



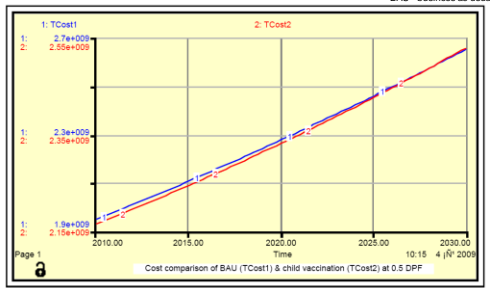
Cost comparison of BAU (TCost1) & child vaccination (TCost2) at 0.75



Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
TCost1(e+6Baht)	2027	2377	2418	2459	2500	2541	2582	2622	2782
TCost2(e+6Baht)	2245	2461	2488	2541	2541	2567	2593	2619	2719

NOTE THAT Y AXIS SCALES ARE NOT THE SAME FOR T1 AND T2

Cost comparison of BAU (TCost1) & child vaccination (TCost2) at 0.5 DPF



Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
TCost1(e+6Baht)	1947	2277	2313	2349	2385	2422	2459	2497	2653
TCost2(e+6Baht)	2165	2331	2349	2368	2387	2406	2426	2446	2529

NOTE THAT Y AXIS SCALES ARE NOT THE SAME FOR T1 AND T2

T cost 1 and 2 at 0.75

Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
TCost1(e+6Baht)	2027	2377	2418	2459	2500	2541	2582	2622	2782
TCost2(e+6Baht)	2245	2461	2488	2541	2541	2567	2593	2619	2719

T cost 1 and 2 at 0.5

Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
TCost1(e+6Baht)	1947	2277	2313	2349	2385	2422	2459	2497	2653
TCost2(e+6Baht)	2165	2331	2349	2368	2387	2406	2426	2446	2529

Regular public campaign (2% concern) and dog population

Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
Dog no. (e+6)	12.0	14.9	15.2	15.4	15.7	16.0	16.3	16.6	17.5
Bitten pop(e+3)	508	595	605	616	626	636	646	659	697

Increase public campaign (more concern to 5%) and dog population

Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
Dog no. (e+6)	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Bitten pop(e+3)	508	582	588	596	604	612	620	629	664

Increase public campaign (more news to 5%) and T cost1 and 2

Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
TCost1(e+6Baht)	2027	2316	2347	2379	2411	2444	2477	2511	2651
TCost2(e+6Baht)	2245	2364	2378	2393	2408	2423	2439	2455	2525

Cost comparison of rabies pre-exposure vaccination with post-exposure treatment in Thai children

Pannipa Chulasingandha, Pakamatz Khawplod, Piyapani Havanond, Henry Wilde Vaccine 2006

- Head to head cost - comparison in children < 14 between (PREP and PEPbooster) and (PEP)
- At which number of biting prevalence, the cost of PREP is equal to PEP

Table 1

Cost equivalence expressed as percentage of dog bite prevalence<sup>a</sup>

Post-exposure regimens	Pre-exposure regimens		
	PREP 1 <sup>b</sup> (%)	PREP 2 <sup>b</sup> (Vaccine 0.5 mL/visit) (%)	PREP 3 <sup>b</sup> (Vaccine 1.0 mL/ampoule) (%)
PEP 1: full dose IM	- <sup>c</sup>	12	6
PEP 1 and HERO	- <sup>c</sup>	7	4
PEP 2: ID 2-2-0-1-1 (vaccine 0.5 mL/visit)	25	4	2
PEP 2 and HERO	- <sup>c</sup>	30	14
PEP 3: ID 2-2-0-1-1 (vaccine 1.0 mL/ampoule)	- <sup>c</sup>	12	7
PEP 3 and HERO	- <sup>c</sup>	6	3
PEP 3 and ERGO	- <sup>c</sup>	- <sup>c</sup>	- <sup>c</sup>
PEP 3 and ERGO	- <sup>c</sup>	14	23
PEP 3 and HERO	- <sup>c</sup>	6	3

<sup>a</sup> Cost equivalence expressed as percentage of dog bite prevalence. Cost for PREP of 100 children plus cost for a later PEP of a out of 100 PREP children is equal to cost for PEP of a non-immunized children. If prevalence is less than a, PEP will become lesser in cost. On the contrary, if the prevalence is higher than a, PREP will become lesser in cost.  
<sup>b</sup> PREP, no immunoglobulin required.  
<sup>c</sup> Equal cost did not occur.

Pre-exposure childhood immunization (EPI program): Cost effectiveness analysis

- Parameters also involve feedback inhibition influenced by community or public concern which result to dog population reduction and in turn affecting dog biting incidence
- Add-on action (mass vaccination since newborn) to PEP
- All the numbers or expenses as calculated by this mathematical program show that Childhood immunization program increases the total annual expenses of immunization (PREP and PEP), but the rate of rise gradually declines and eventually equals to the amount of PEP expense (without childhood immunization) in 15-16 years. If the number or density of dogs (ratio of dog: household) can be manipulated (from 0.75 to 0.5 per household) with childhood immunization implemented, the time required for total expenses to come down to those of PEP alone will be achieved in 13 years.
- Public concern/action also intensifies the effect

## Favorable considerations (1)

- Effective and sustainable dog vaccination and population control have not been successful and the high prevalence of dog rabies, especially in community dogs, remains unacceptable.
- Childhood rabies pre-exposure immunization (PREP) should be considered for high rabies prevalence regions where there is a high risk for children < 14 years of age.
- Time of administering rabies PREP may be possible by one at birth (maternal antibody?) and 2 months or another at 2 and 4 months.
- The technique of ID injection is well known and widely practiced in most developing countries (BCG at birth etc).
- The need for the third dose may not be necessary (?).

## Favorable considerations (2)

- Studies have shown that mass pre-exposure vaccination can be done. PREP at 2, 4 months and 1 year.
  - 1 - 5 year follow up- no interference with other vaccines
  - IM or ID equally effective
  - Maintenance of antibody level was shown in more than half after 5 years
- Re-exposures are common in childhood . No need for immunoglobulin (RIG)
- Booster is possible with 1 visit 4 site ID

## Unfavorable considerations (3)

- It is not certain whether all children will receive all 2 or 3 doses of rabies for PREP.
- Solving an old problem by starting a new one. Further aggravate ignorance or lack of interest in dog vaccination and population control.
- Once re-exposure happens, it may be difficult to know who has already received PREP.
- Need a rapid reliable and inexpensive test for rabies antibody to determine whether a patient with doubtful history of PREP has antibody or may need a full course of PEP with RIG.
- Impossible to determine the efficacy of a universal PREP regimen due to the low incidence of rabies (< 20 among 70 million in Thailand).
- Policy makers need to be convinced that childhood immunization is cost-effective.