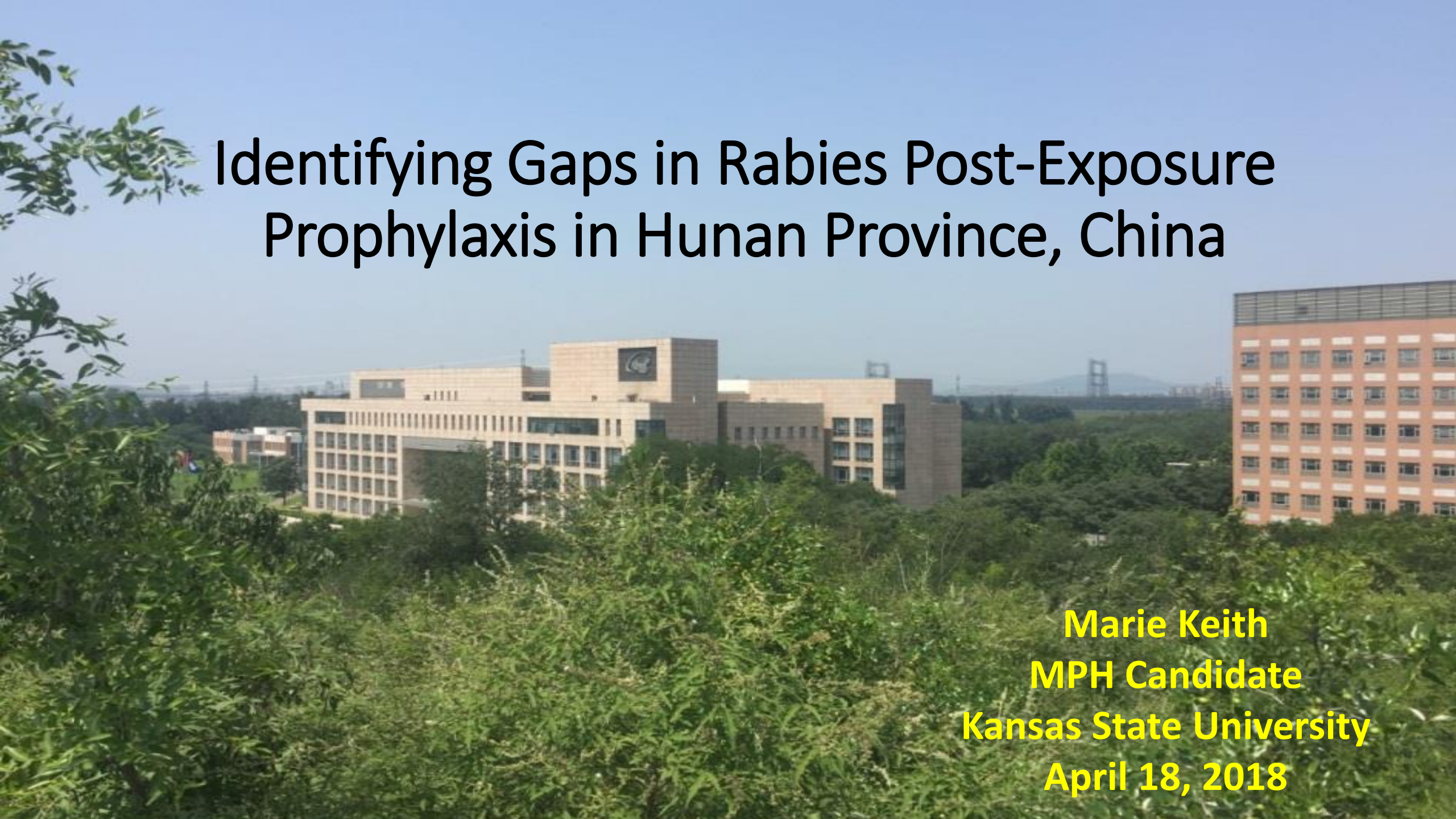


The background of the slide is a photograph of a university campus. In the foreground, there are dense green bushes and trees. In the middle ground, there are several modern university buildings with large windows and flat roofs. One building has a circular logo on its facade. To the right, there is a taller, more traditional brick building. In the far background, a bridge and distant hills are visible under a clear blue sky.

Identifying Gaps in Rabies Post-Exposure Prophylaxis in Hunan Province, China

Marie Keith
MPH Candidate
Kansas State University
April 18, 2018

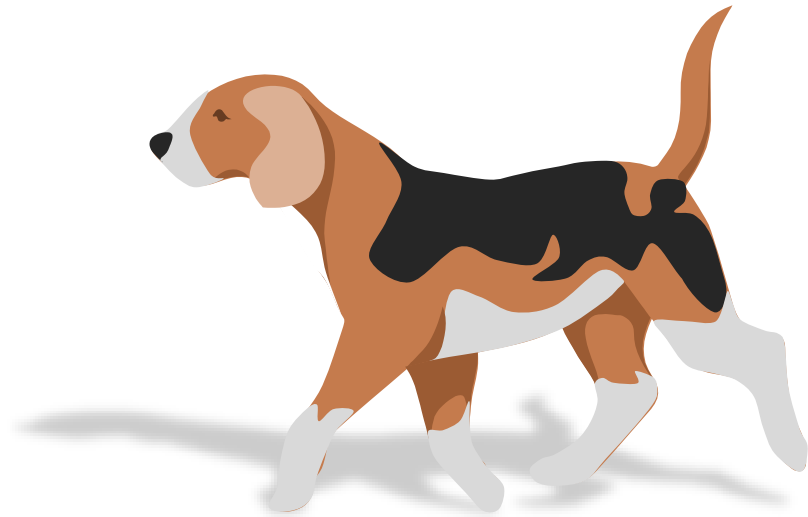
The Global Burden of Canine Rabies

Hamson et al. 2015

Est. 59,000 deaths annually
Under-reporting

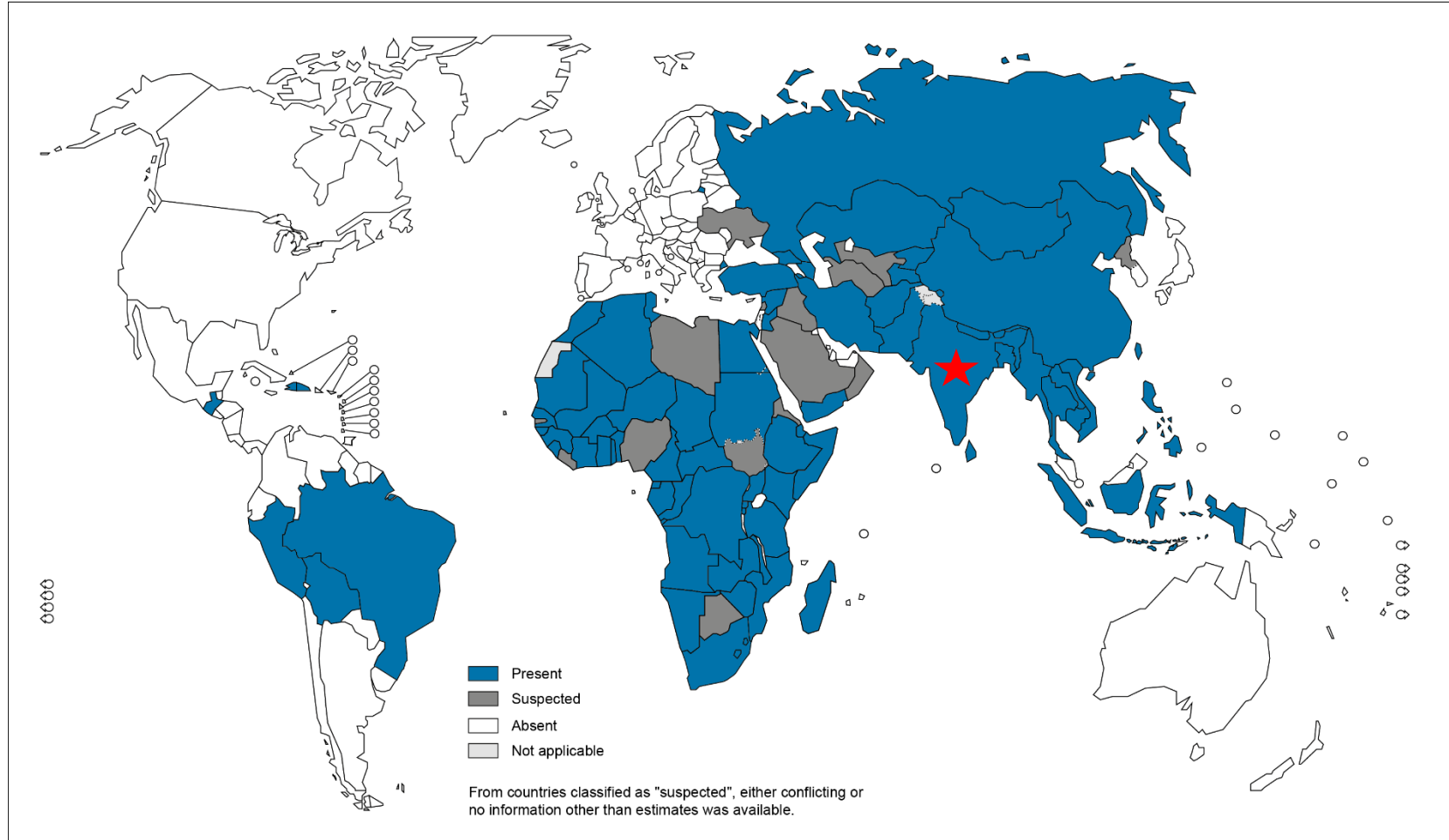
> 3.7 million DALYs/ year

8.6 Billion USD/ year
PEP costs: 20%
Income lost while seeking PEP: 15%



Global Epidemiology

Presence of dog-transmitted human rabies based on most recent data points from different sources, 2010-2014



Rabies in China

- 2nd highest burden globally
 - 1950 – 2010: avg 2,037 cases/year
 - 2007: 3,300 cases
- Risk Factors
 - Male
 - Rural
 - Farmer
 - < 15 or > 50
 - Dog bite
 - Southern provinces
- 12 – 15 million doses PEP/year



Rabies Prevention & Biologics

#1: Eradicate canine rabies

#2: Appropriate risk-based PrEP and PEP

Anti-Rabies Vaccines (ARVs)

- Nerve Tissue Vaccines: available since 1885
- Cell Culture Vaccines: available since 1970s

Rabies Immunoglobulin (RIG)

- Human RIG
- Equine RIG – misconceptions about safety

> 29 million people receive PEP annually in rabies endemic regions

When used appropriately, rabies PEP is extremely safe & effective

WHO Exposure Categories and Treatments

Categories of contact with suspect rabid animal	Activity/Wound Description	Post-exposure prophylaxis measures
Category I	Touching or feeding animals, licks on intact skin	None
Category II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Immediate vaccination and local treatment of the wound (ARVs)
		Immunocompromised persons [§] with a Category II exposure should also receive rabies immunoglobulin. (ARVs + RIG)
Category III	Single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membranes with saliva from licks, contact with bats.	Immediate vaccination and administration of rabies immunoglobulin; local treatment of the wound (ARVs + RIG)

[§]Immunocompromised persons include any patient with an illness such as HIV, TB or cancer or other illnesses known to suppress the immune system. Also included are patients that have been on an immunosuppressive medication for any reason prior to a rabies exposure.

WHO-Approved PEP Vaccine Regimens

Intramuscular Route (0.5 – 1.0 ml at each site, depending on vaccine)	
5-dose (“Essen”) Regimen	1 dose each on days: 0, 3, 7, 14, 28
4-dose (“Zagreb”) Regimen (also referred to as “2-1-1”)	1 dose at each of 2 sites on day 0; 1 dose each on days: 7, 21
Modified 4-dose Regimen [‡] + RIG [*]	1 dose each on days: 0, 3, 7, 14 *RIG <u>must</u> also be administered [‡] May not be used on sick or immunocompromised persons [§]
Intradermal Route (0.1 ml at each of 2 sites)	
Updated Thai Red Cross Regimen	1 dose at each of 2 sites on days: 0, 3, 7, 28
PEP for patients who have already received Pre-Exposure Prophylaxis (PrEP)	
Intramuscular	1 dose each on days: 0, 3
Intradermal	1 dose at each of 4 sites on day 0

**Minimum 3
visits to PEP
clinic**

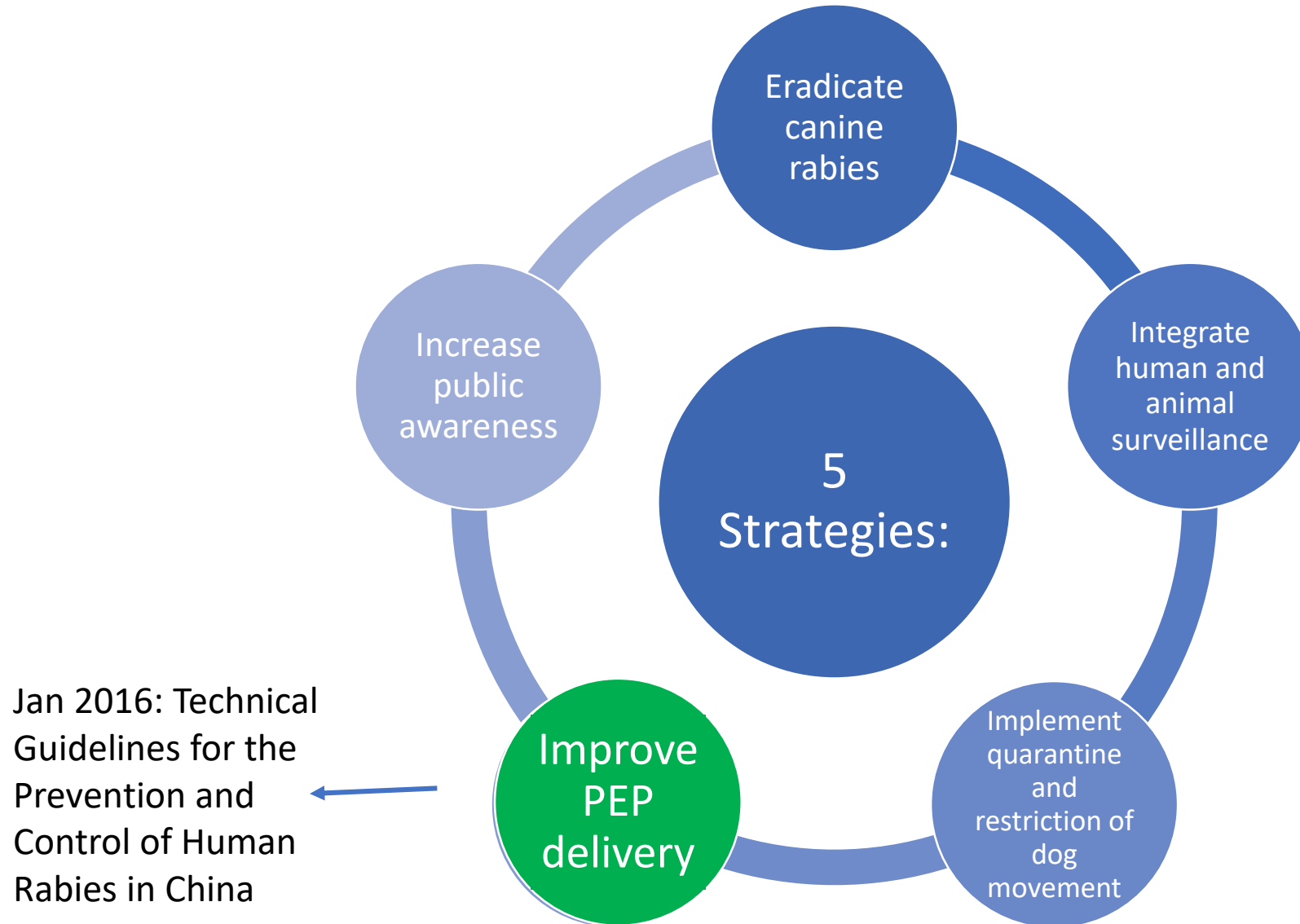
**Significant volume
reduction with ID
compared to IM**

China Centers for Disease Control & Prevention

- Formed in 2002 (SARS)
- Goals:
 - (1) disease prevention and control
 - (2) scientific research
 - (3) workforce development
- ~ 2,100 staff

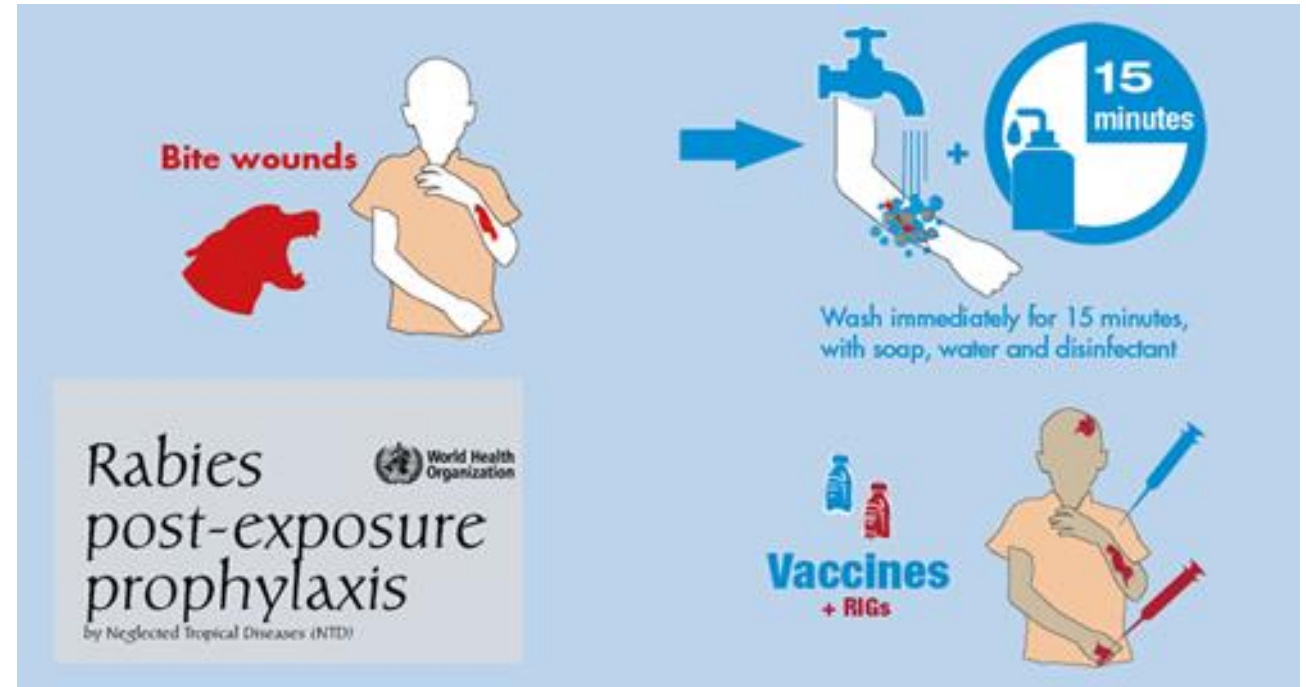


China CDC & Rabies: 0 by 2025



PEP Failures in China

- 12 – 15% rabies cases *did* visit a PEP clinic
- What went wrong?
 - Compliance?
 - Inappropriate delivery of PEP?



**Assess this via a
Pilot Study**

Study Goals & Questions:

Develop tools to assess preparedness of rabies PEP clinics, staff training, PEP delivery

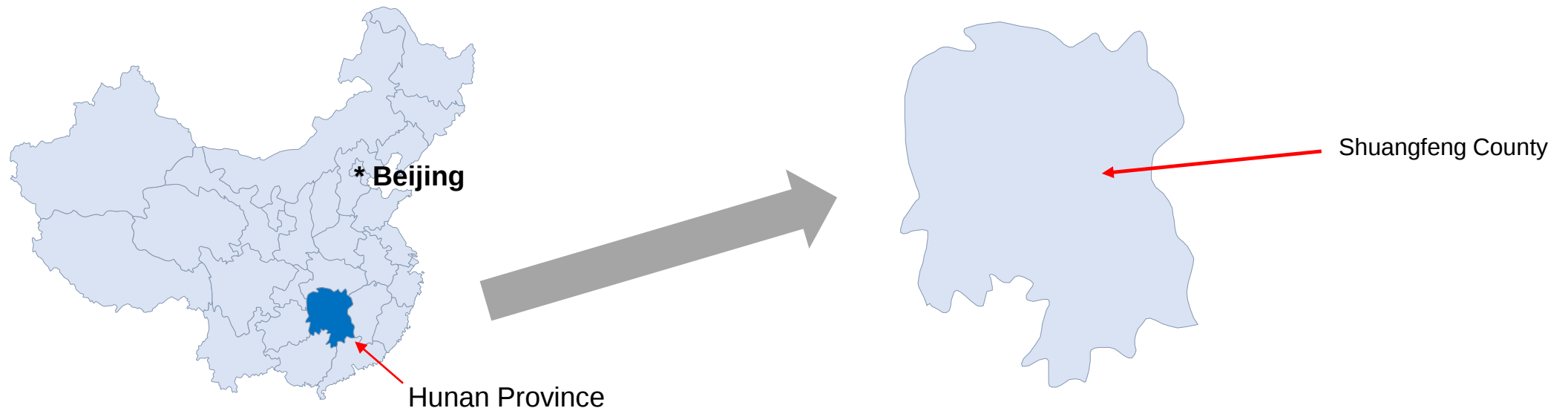
- Resources at rabies PEP clinics?
- Demographics of persons seeking PEP?
- Are exposures accurately classified by healthcare workers?
- Is the appropriate treatment protocol selected?

Identify Gaps in PEP knowledge and practices

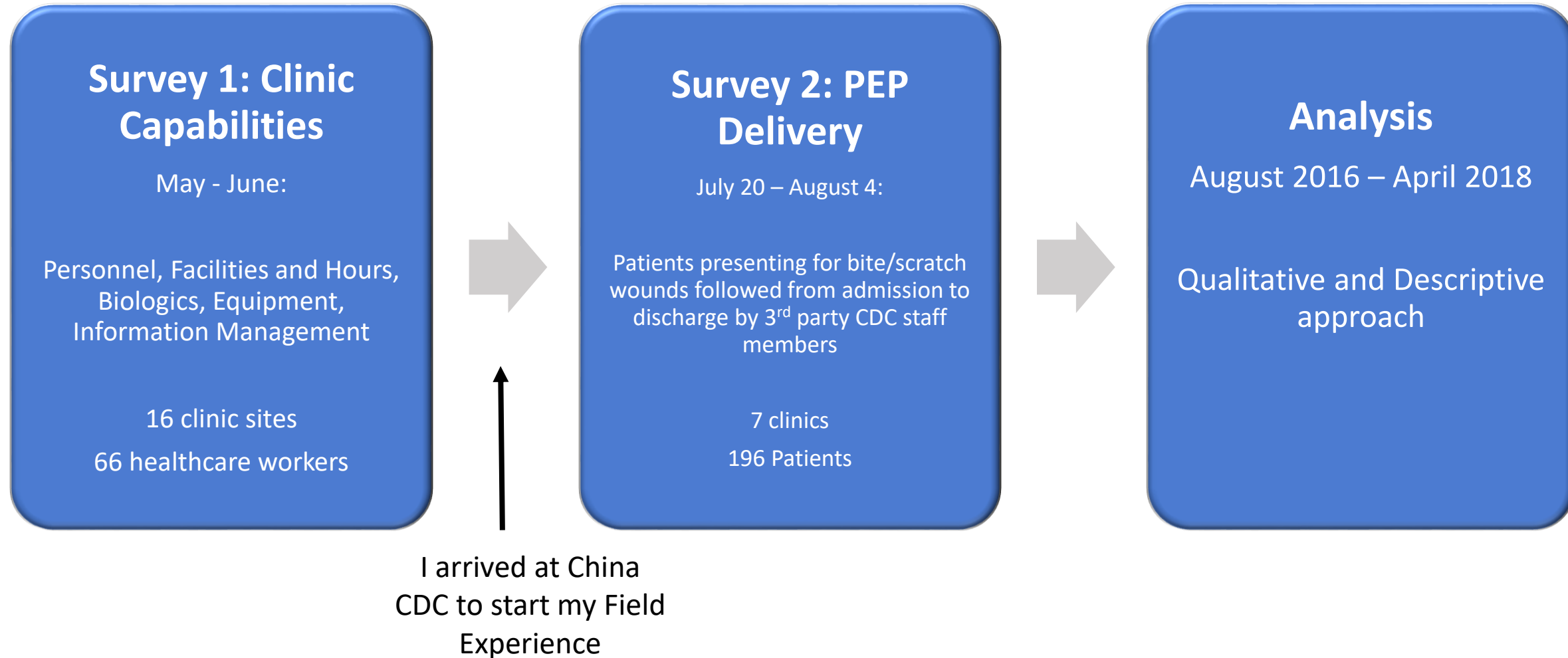
Pilot Study: Shuangfeng County, Hunan Province

(May – August, 2016)

- High incidence of rabies
- Pop. 850,000
- 5,000 courses of PEP (588/100,000 persons) annually



Pilot Design: Two Survey Assessment



Survey 1: Clinic Capabilities

Rabies Biologics and Adverse Event Preparedness

Rabies Biologics	Equipment & Emergency Preparedness
• Regimen: Essen (5-dose IM) • ARVs Cost: 290 – 375 RMB (\$46 - \$59) per person • RIG Supply: Only 1/16 clinics had RIG in stock (HRIG) • RIG cost: 250 RMB/vial (\$40)	• Refrigerators: 16/16 • Epinephrine: 15/16 • Dexamethasone: 13/16



Survey 2: PEP Delivery

1. Intake Inquiry

- Exposure source & Method
- Wound
- HCW Assessment

2. Wound Care

- Duration
- Use of Soap and disinfectant

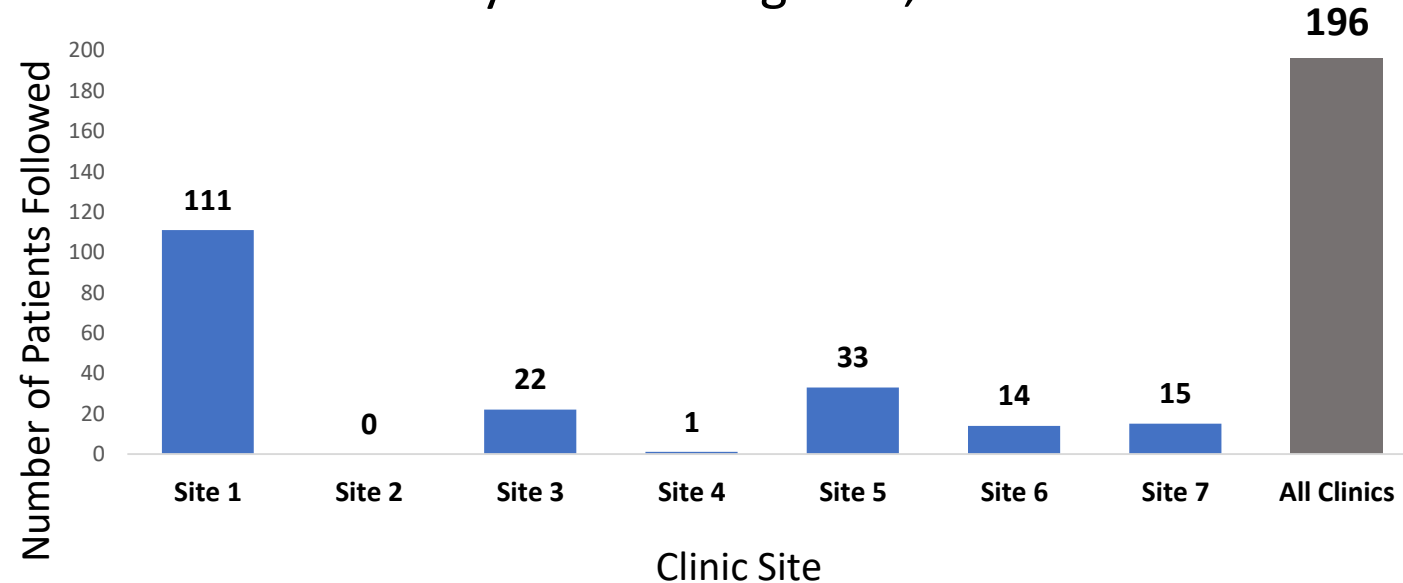
3. Anti-Rabies Vaccines

- Was the first dose of ARV administered? If not, why?
- Was the vaccine expired?

4. Rabies Immunoglobulin

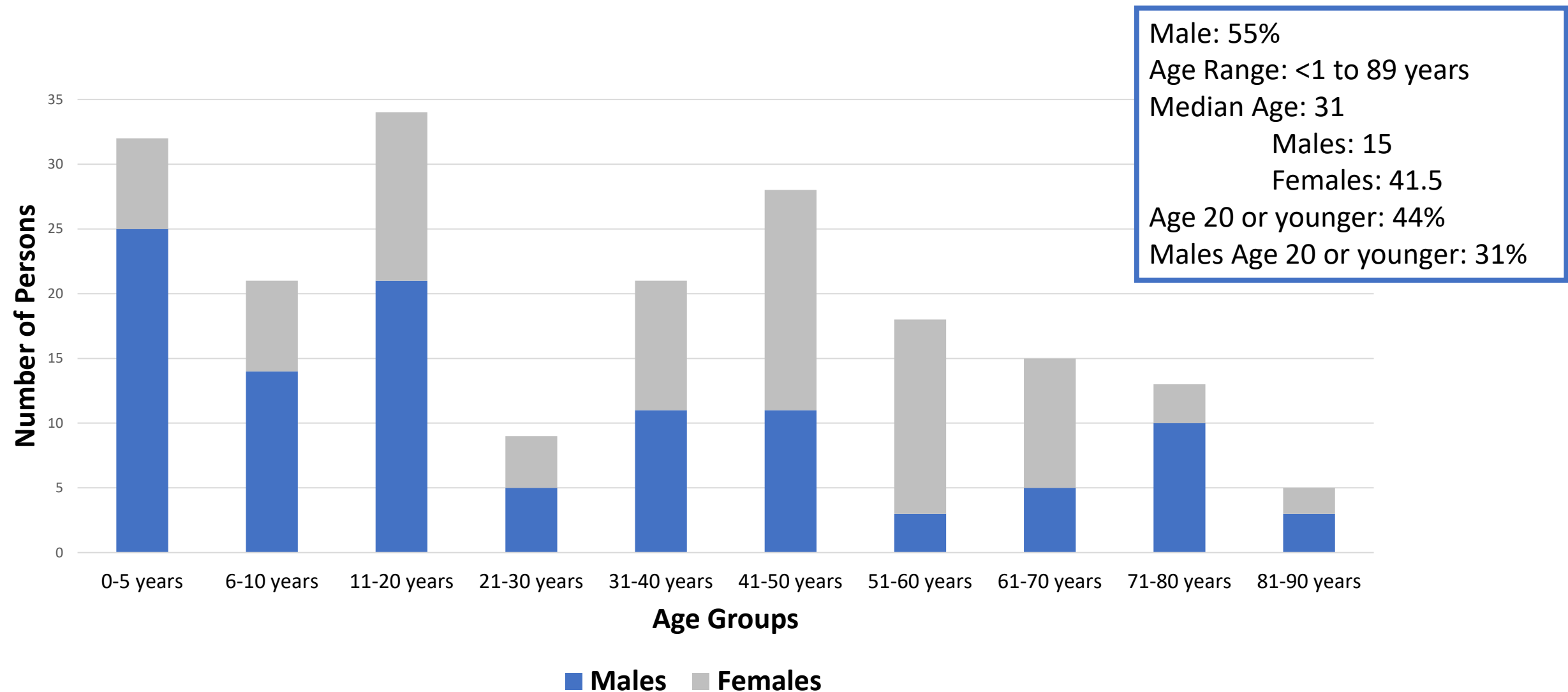
- Was RIG administered? If not, why?
- Dose?

Patients Presenting for Bite/Scratch Wounds
July 20 and August 4, 2016



Survey 2: PEP Delivery

Demographics of Patients Presenting for Bite/Scratch Wounds



Survey 2: PEP Delivery

Wound Source: Species, Ownership, Animal's Vaccination Status

		Number	% of Total	% of Domestic animals
Dogs		140	71.4	
	<i>Owned by patient's family</i>	67	34.2	
	<i>Owned by someone else</i>	27	13.8	
	<i>Unknown</i>	15	7.7	
	<i>Not inquired</i>	31	15.8	
Cats		38	19.4	
	<i>Owned by patient's family</i>	26	13.3	
	<i>Owned by someone else</i>	2	1.0	
	<i>Unknown</i>	2	1.0	
	<i>Not inquired</i>	8	4.1	
<i>Domestic animals (owned dogs and cats)</i>		122	62.2	
	<i>Vaccinated</i>	1		0.8
	<i>Unvaccinated</i>	2		1.6
	<i>Not inquired</i>	119		97.5
Rats		16	8.2	
Human		1	0.5	
<i>Unknown</i>		1	0.5	

Does it matter if
the animal is
vaccinated?

Survey 2: PEP Delivery

Exposure Method and WHO Categorization

WHO Exposure Category	Exposure Method	Number of Patients	%	Number of Patients	%
I	Touching/feeding animals	0	0	5	2.5
	Lick on intact skin	4	2		
	“Other”	1	0.5		
II	Nibbling at exposed skin	35	17.9	103	52.6
	Minor scratch or abrasion without bleeding	68	34.7		
III	Penetrating skin bite(s) or scratch(es)	87	44.4	88	44.9
	Lick on area of broken skin	1	0.5		
	Open wound or mucous membrane contamination	0	0		

Survey 2: PEP Delivery

Exposure Categorization: WHO compared to HCW

WHO Category	# Patients	Exposure Category applied by HCW	# Patients	% of Category	% of Total
I	5	I	2	40	1
		II	3	60	1.5
		III	0	0	0
II	103	I	9	8.7	5
		II	94	91.3	48
		III	0	0	0
III	88	I	3	3.4	1.5
		II	34	38.6	17
		III	51	58	26

**25% of Patients
mis-categorized**

**23.5% of Patients
under-categorized**

Survey 2: PEP Delivery

Relevant Medical History-Taking

HCW asked about:

58%	patient's rabies vaccination status
9.2%	possible immunocompromised status due to disease (HIV, TB, cancer)
0%	use of immunosuppressive drugs
13%	history of drug/vaccine allergies

Survey 2: PEP Delivery

Wound Care Summary

	# of patients whose wound was washed (%)		Appropriately washed (%)
<i>WHO Category II and III (191 patients)</i>	by HCW:	1 (0.5)	0 (0)
	by patient/accompanying person:	151 (79)	95 (49.7)
	at another facility:	4 (2)	?
	at home:	26 (13.5)	4 (2.1)
	Not washed:	9 (5)	N/A
	Total: 99/191 = 51.8%		
<i>HCW Category II and III (182 patients)</i>	by HCW:	1 (0.5)	0 (0)
	by patient/accompanying person:	140 (77)	85 (47)
	at another facility:	4 (2)	?
	at home:	27 (15)	6 (3)
	Not washed:	10 (5.5)	N/A
	Total: 91/182 = 50%		

Survey 2: PEP Delivery

ARVs Initiated: Improper Patient Selection

<i>Exposure Type</i>	<i># Total Patients</i>	<i># Patients receiving ARV (%)</i>
<i>WHO Category I</i>	5	5 (100)
<i>WHO Category II</i>	103	103 (100)
<i>WHO Category III</i>	88	87 (99)
<i>HCW Category I</i>	14	14 (100)
<i>HCW Category II</i>	131	131 (100)
<i>HCW Category III</i>	51	50 (98)
<i>Total Patients</i>	196	195 (99)

2.5% of Patients
incorrectly received ARVs

HCWs incorrectly
selected 7% of patients
to receive ARVs based on
their own evaluation of
the exposure

2/195 (1%) vaccines administered were past the expiration date.

Survey 2: PEP Delivery

Patients Receiving RIG by Exposure Category (WHO and HCW)

Exposure Category	# Total Patients	# Receiving RIG	# NOT Receiving RIG
WHO Category I	5	5	0
WHO Category II	103	103	0
(II – Immunocompetent)	(101)	(101)	(2)
(II – Immunocompromised)	(2)	(2)	(0)
WHO Category III	50*	29	21

43% of patients who should have received RIG according to WHO did.

69% of patients who should have received RIG according to HCW did.

*1 of these patients had previously been vaccinated for rabies and did not require RIG.

Survey 2: PEP Delivery

Why was RIG not administered?

	Proportion of Patients who did Not Receive RIG (%)	HCW did not recommend RIG (%)	Patient did not consider RIG to be necessary (%)	RIG not available at the clinic (%)	RIG was cost prohibitive (%)	Patient was referred elsewhere (%)
Category I (HCW)	14/14 (100)	2 (14.3)	10 (71.4)	2 (14.3)	-	-
Category II Immunocompetent (HCW)	126/126 (100)	104 (81)	10 (8)	11 (8)	1 (1)	-
Category II Immunocompromised (HCW)	5/5 (100)	2 (40)	-	2 (40)	1 (20)	-
Category III (HCW)	13/51 (25)	7 (54)*	5 (38)	-	-	1 (8)

*1 was previously vaccinated

30% of cases in which RIG was not administered, a non-valid reason was cited by the HCW



HCWs do not understand the rationale behind RIG administration

Survey 2: PEP Delivery

Patients Receiving Adequate HRIG Dose

- HRIG: Body Weight-dependent dose (20 IU/kg)
- **63%:** Body weight of patient measured (24/38)
 - **54%:** Correct volume administered according to weight (13/24)
 - **46%:** Patient under-dosed in cases where body weight was measured (11/24)

14.6% of patients who should have received RIG according to WHO guidelines received a sufficient dose of RIG.

Project Limitations

- Observational Study → systematic bias
 - Study site selection
 - Information bias: selective recall of patients
 - Selection bias: patients had to voluntarily agree to be followed
 - Quality of observer information
- Pilot Study
- Sample size
- Impacts of flooding on PEP-seeking behaviors?
- Length

Gaps Identified

Clinic equipment and preparedness

Recognizing exposure levels

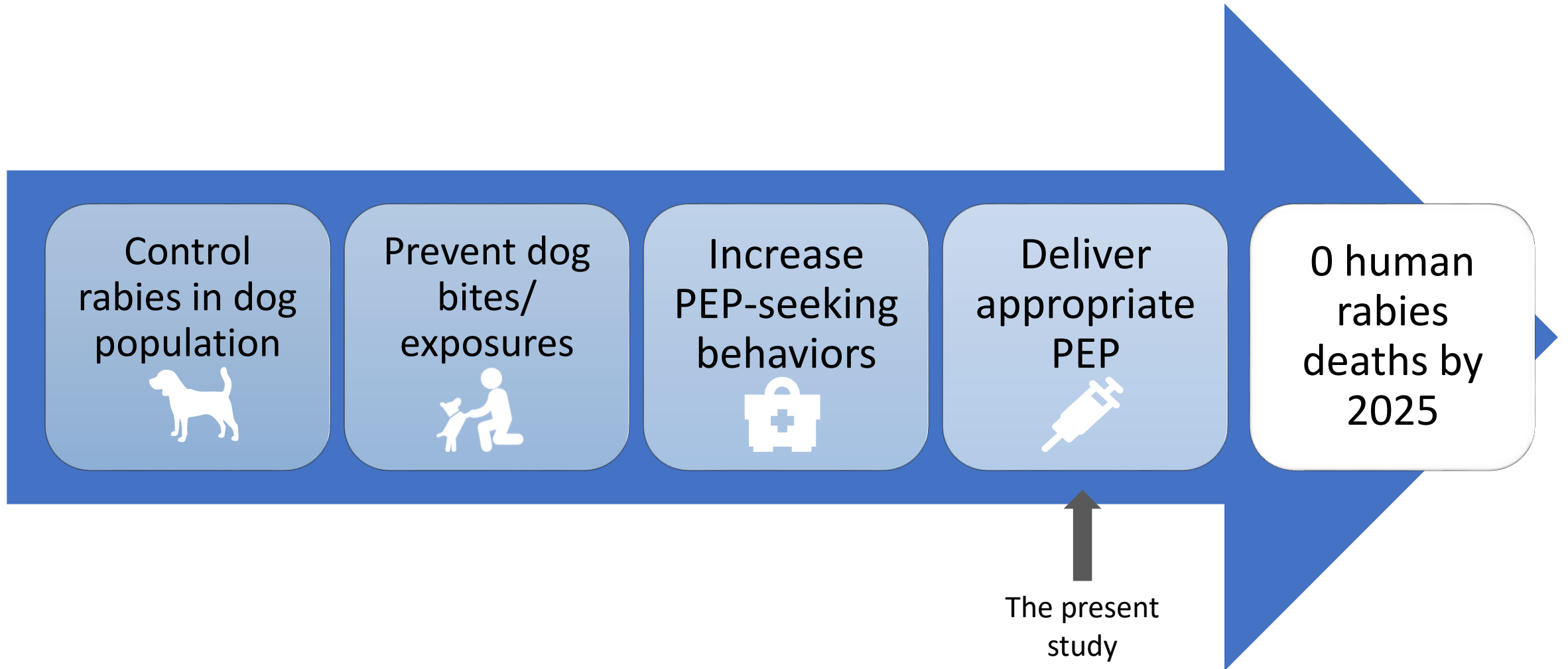
Taking Relevant Medical History

Selecting risk-based treatment plans

Administering PEP treatments

Communicating risks to patients

Rabies Control: The Bigger Picture



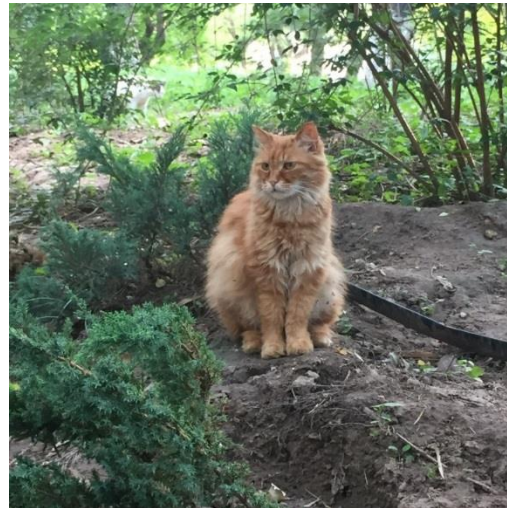
Acknowledgments

- Dr. George Gao and Dr. Li Yu, China CDC
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- KSU CVM International Programs Office
- KSU Master of Public Health Program



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Thank You!

