Pandemic Influenza Preparation Update

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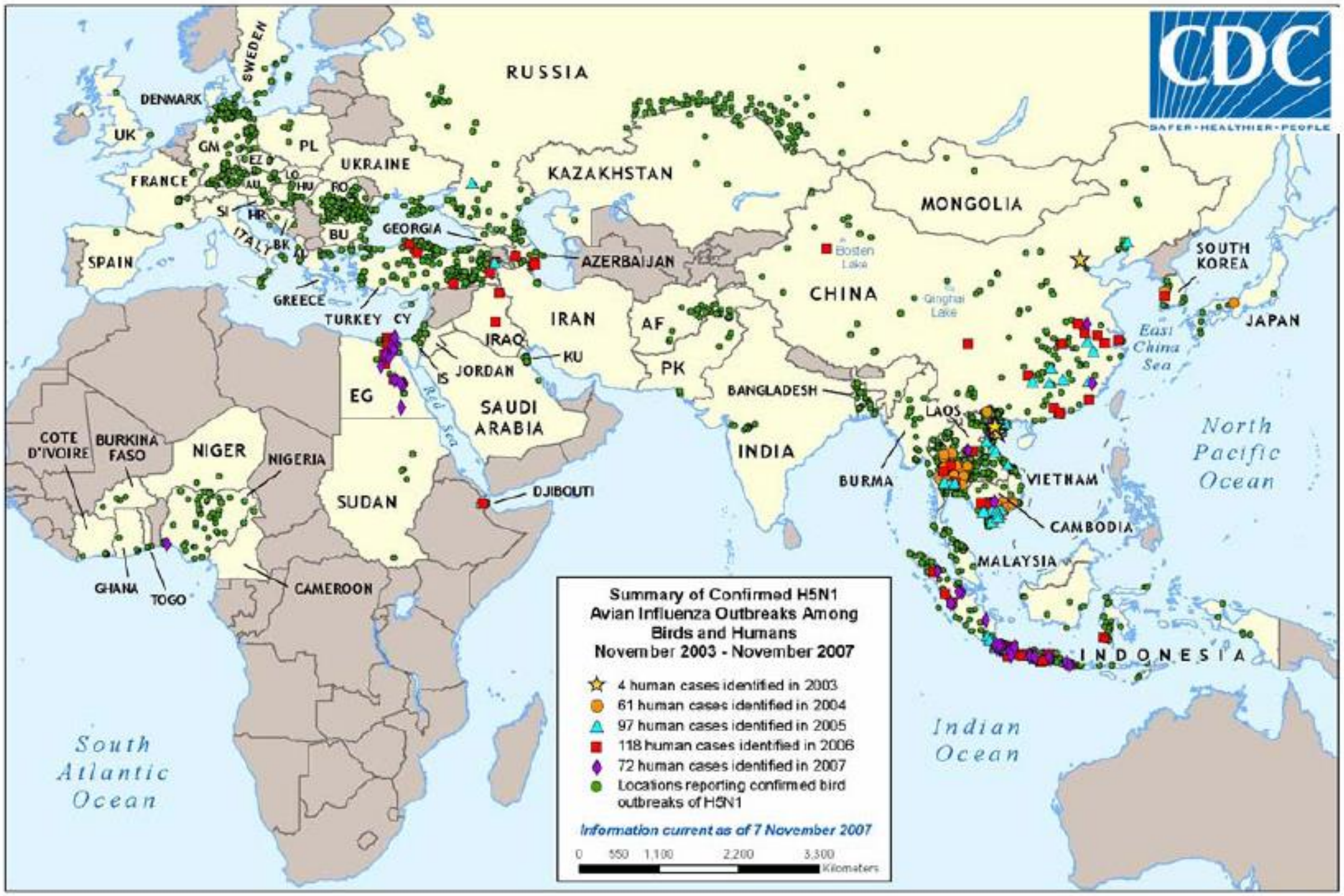
Force Health Protection and Readiness
December 2007

Agenda

- Current status of H5N1
- Antivirals
  - Resistance
  - National plan
  - DoD plan
- Modeling
  - Vaccine
  - Antivirals


CDC
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RUSSIA
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SWEDEN
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COTE D'IVOIRE
GHANA
TOGO
CAMEROON
East China Sea
North Pacific Ocean
Indian Ocean
South Atlantic Ocean
Summary of Confirmed H5N1 Avian Influenza Outbreaks Among Birds and Humans
November 2003 - November 2007
4 human cases identified in 2003
61 human cases identified in 2004
97 human cases identified in 2005
118 human cases identified in 2006
72 human cases identified in 2007
Locations reporting confirmed bird outbreaks of H5N1
Information current as of 7 November 2007
0 550 1,100 2,200 3,300 Kilometers

OIE confirmed H5N1 Activity in Poultry and Wild Birds in 2007

- Afghanistan
- Bangladesh
- Cambodia
- China
- Czech Republic
- France
- Germany
- Ghana
- Hong Kong
- Hungary
- India
- Japan
- Republic of Korea
- Kuwait
- Laos
- Malaysia
- Myanmar
- Pakistan
- Russia
- Saudi Arabia
- Thailand
- Togo
- Turkey
- United Kingdom
- Vietnam

The Year in Birds – H5N1 Activity for 2007

JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC

Global Count – 60 Countries

Germany, Myanmar, Pakistan further outbreaks in poultry

UK and Kuwait report first findings in poultry – previously reported wild birds

France outbreak in wild birds

Russia, China, Germany, Vietnam more poultry outbreaks

Ghana reports

Now 59 Countries

Germany – wild bird outbreak

Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO in 2007 as of 12 November 2007

Country	Cases	Deaths
Indonesia	38	33
Egypt	20	5
Viet Nam	7	4
China	3	2
Lao PDR	2	2
Cambodia	1	1
Nigeria	1	1

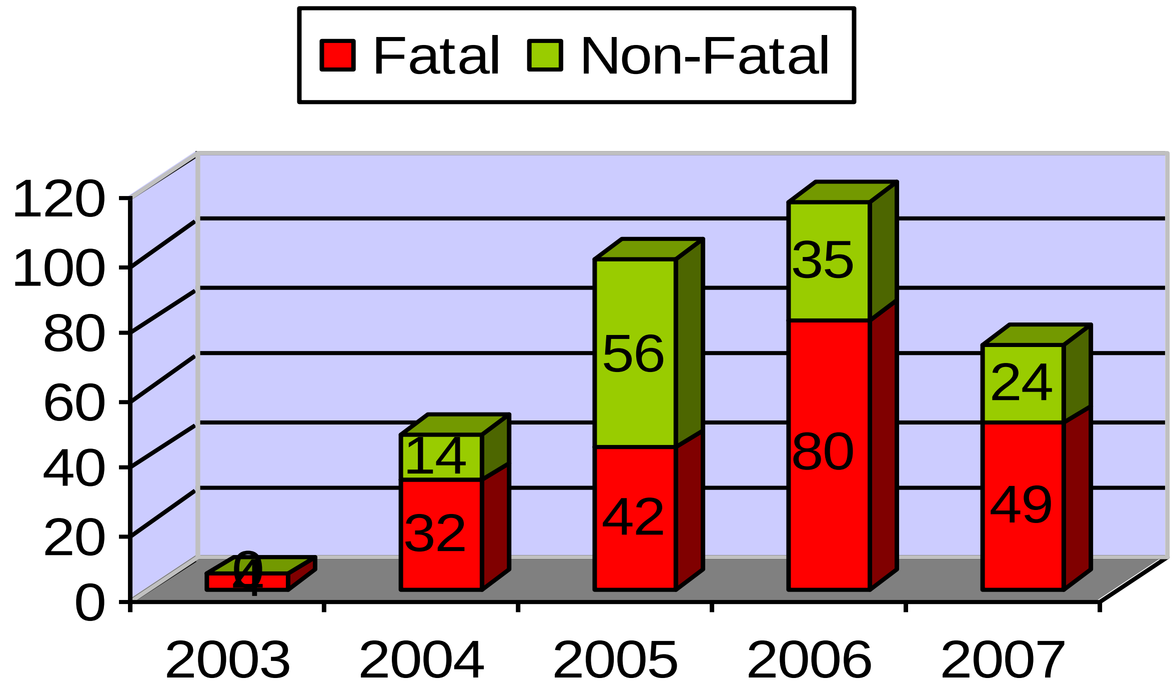
Indonesia

- Remains a hot spot with the highest number of new cases for 2007
- Sole source of new cases of Clade 2.1 disease
- GOI continues to refuse to share samples
- Mitigation measures continue to be hampered due to decentralized government (public health system)

Egypt

- Second highest case rate
- Clade 2.2
- Lowest mortality rate
- Effective control measures in place
  - Pandemic plan a model for the area
  - Extensive communication program facilitates early recognition and treatment and improved survival
  - Effectively addressing backyard poultry without changing cultural practices

Human Cases H5N1 2003-2007*



* WHO November 14, 2007

Antivirals

Adamantane Resistance Among H5N1 Viruses

Genetic Group		# Resistant	# Tested	% Resistance
Clade 1	Vietnam-like	25	26	96
Clade 2.1	Indonesia-like	61	71	86
Clade 2.2	Qing Hai- like	2	33	6
Clade 2.3	Anhui- like	3	31	10
Total		91	161	57

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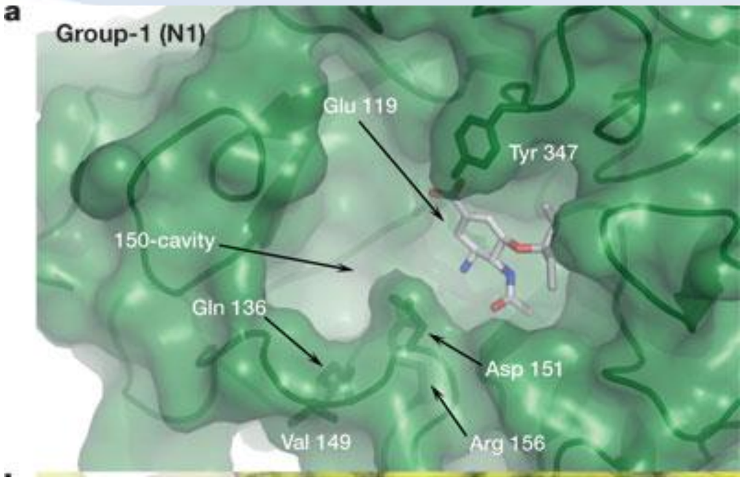
Neuraminidase Resistance

- Represents 8% of samples tested
- Resistance emergence (H274Y) or reduced susceptibility (N294S in Egypt)
- Uncertain of clinical significance
- Molecular markers not well defined
- Differences in NAI susceptibility among A(H5N1) isolates
  - IC_{50}s: clade 1 is 6 fold <H1N1 < 3-5 fold clade 2

New Neuraminidase Inhibitors in H5N1 viruses

- Novel mutations at
  - 136 (human)
  - 150 (avian)
- Potential resistance to
  - Oseltamivir
  - Zanamivir
  - Peramivir



Nature 443, 45-49(7 September 2006)
doi:10.1038/nature05114

Oseltamivir & Hospitalized Patients

- Hospitalized with laboratory confirmed influenza
- 327 adults
  - Median age 77 (15-98)
  - 51% male
  - 75% chronic underlying disease
  - 59% presented to ER within 48hr of symptoms
  - 16% ICU
  - 8.3% died
  - 89% received antibacterial therapy
  - 32% received oseltamivir
  - Treatment with oseltamivir associated with a significant reduction in mortality (OR 0.21 95% CI 0.06 – 0.80)

Antiviral Therapy and Outcomes of Influenza Requiring Hospitalization in Ontario, Canada Allison McGeer, Karen A. Green, Agron Plevneshi, Altynay Shigayeva, Nilofar Siddiqi, Janet Raboud, Donald E. Low, and for the Toronto Invasive Bacterial Diseases Network

Draft National Antiviral Strategy

- Proposes:
  - Increase stockpile to 200M treatment courses (current target 81M now at 37M)
  - Outbreak prophylaxis in certain health care settings
  - Outbreak prophylaxis for emergency services
  - Household post exposure prophylaxis
- Now in public/stakeholder engagement process
- US production capacity 80M/yr
  - If adopted will take a few years to meet goal

Draft DOD Policy Addendum

- Increases oseltamivir stockpile to 4 million treatment courses
- Establishes local stockpiles to = 30% of population at risk for each GeoCOCOM
- Initiates post exposure prophylaxis mitigation strategy
- Maintains treatment and selected outbreak/operational prophylaxis strategies

Modeling Efforts

NIH Sponsored Modeling Efforts Indicate:

- Being a member of a household containing an influenza case is the largest single risk factor for being infected
- Antiviral post-exposure prophylaxis of household contacts is effective in reducing attack rates by 1/3 and peak attack rates by 50%.
  - Requires a robust stockpile
- Unless treatment can be initiated on day 1 there is little impact on community infection rates
- Non-Pharmaceutical Interventions alone may reduce attack rate by ½ to 1/3

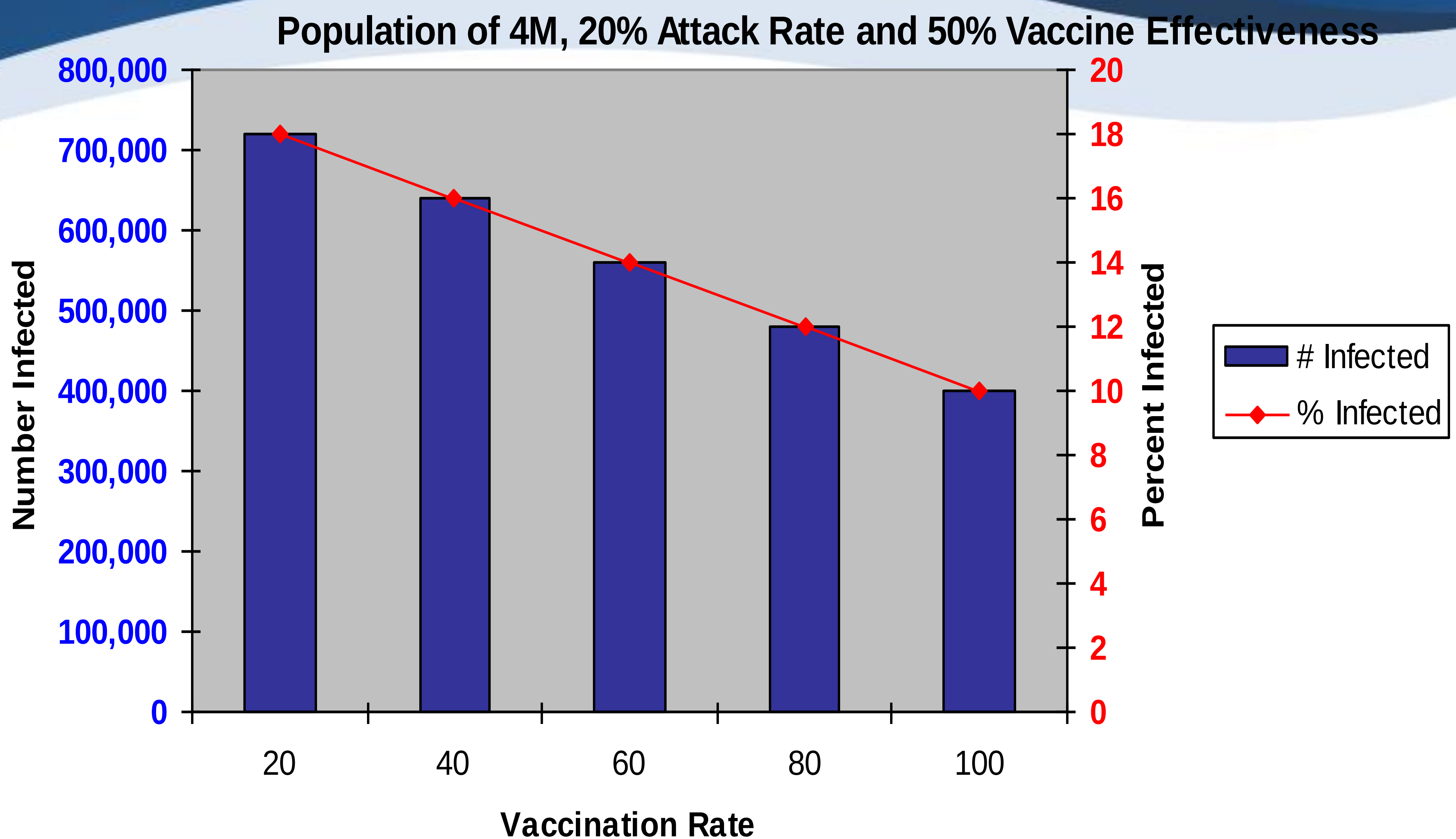
DoD Modeling Efforts

- DTRA model that addressed impact of pandemic influenza vaccine
  - Impact of 0 vs 100% vaccination rate
  - 30% attack rate, vaccine with 30% effectiveness
- Rural installation:
  - 32% infected without vaccine
  - 17% infected with 100% vaccine coverage
- Urban installation:
  - 28% infected without vaccine
  - 15% with 100% immunization
- Lower rates if sequestration is employed
- No herd immunity – only those vaccinated are protected

HA Modeling

- Using basic DTRA computational methods
- Estimates derived with the following variables:
  - Attack Rates of 30, 20, 10%
    - Three assumptions: no, limited and effective community mitigation
  - Vaccine Effectiveness of 30, 50, 80%
    - Reflects unadjuvanted unmatched vaccine, unadjuvanted matched vaccine and adjuvanted vaccine or matched vaccine after priming

Effect of Variable Vaccination Rates on Number and Percent Infected



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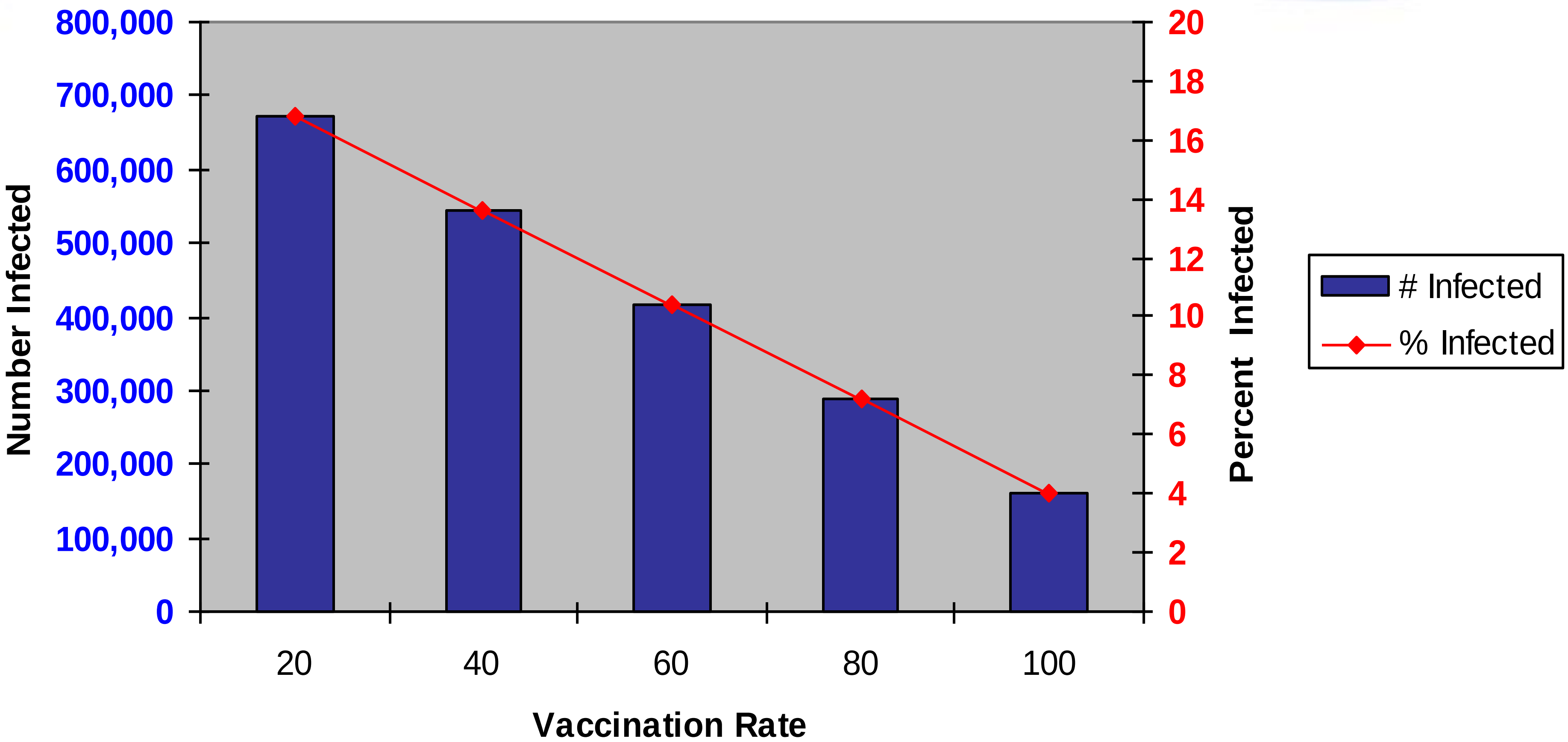
Effect of Variable Vaccination Rates on Number and Percent Infected

Population of 4M, 20% Attack Rate and 80% Vaccine Effectiveness



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Impact of Vaccine with Variable Effectiveness and Attack Rates

- As attack rates (AR) decreases so does the number of cases prevented with vaccine
- As vaccine effectiveness (VE) increases greater reduction in % infected

Decrease in % infected for every 20% vaccinated			
	10% AR	20% AR	30% AR
30% VE	0.6	1.2	1.8
50% VE	1	2	3
80% VE	1.6	3.2	4.8

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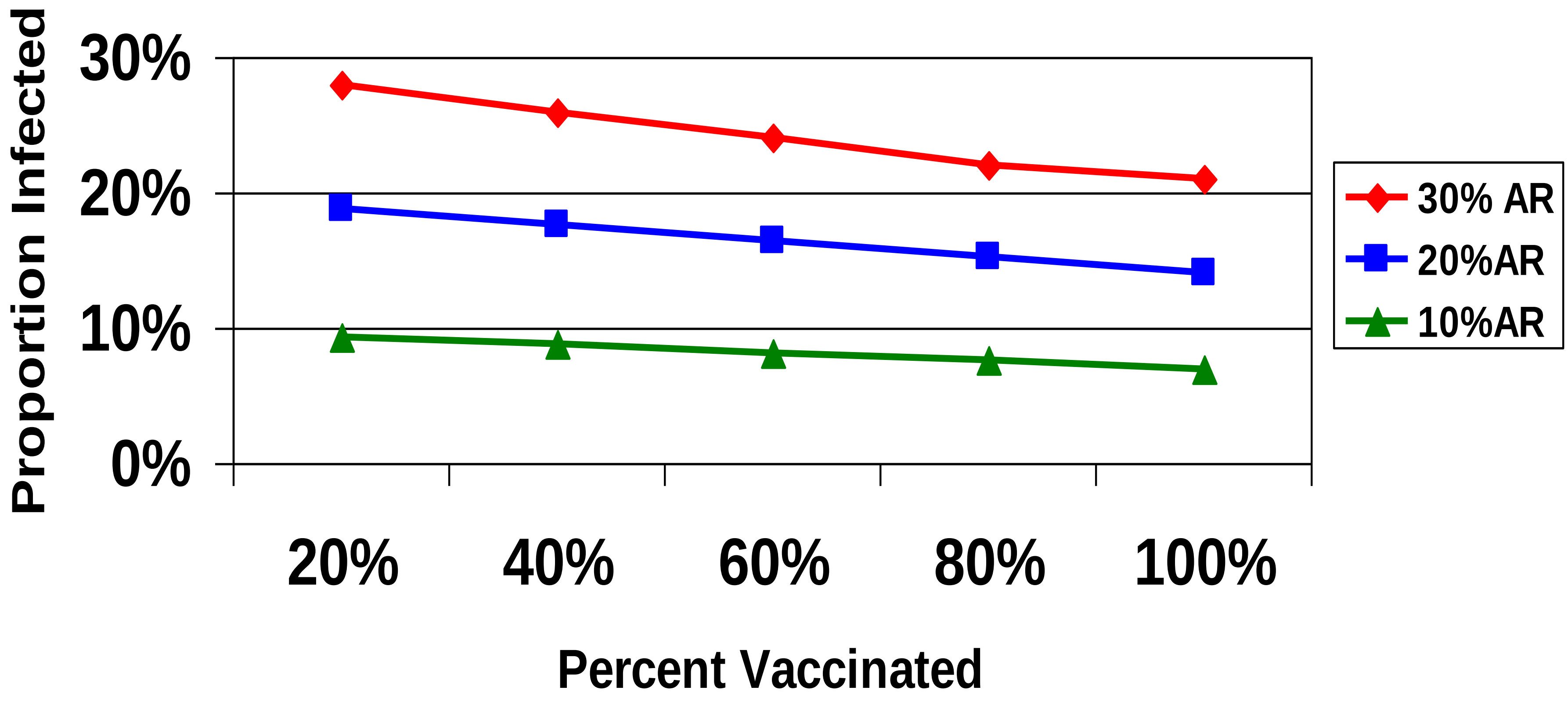
30% Vaccine Effectiveness
Effect of Variable Attack Rates (AR) and Vaccination Rate on Proportion of the Population Infected



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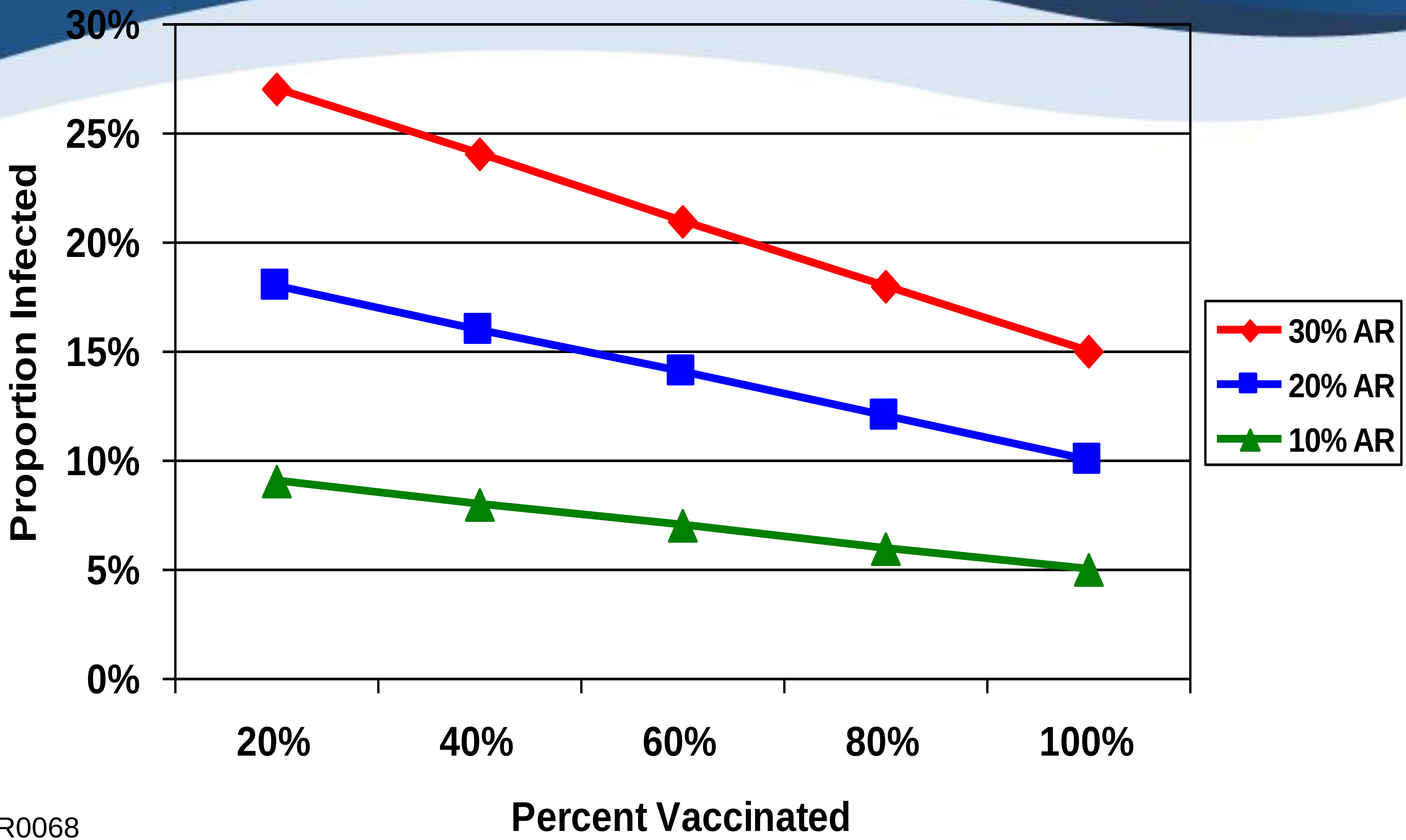
50% Vaccine Effectiveness
Effect of Variable Attack (AR) and Vaccination Rates on the Proportion of the Population Infected



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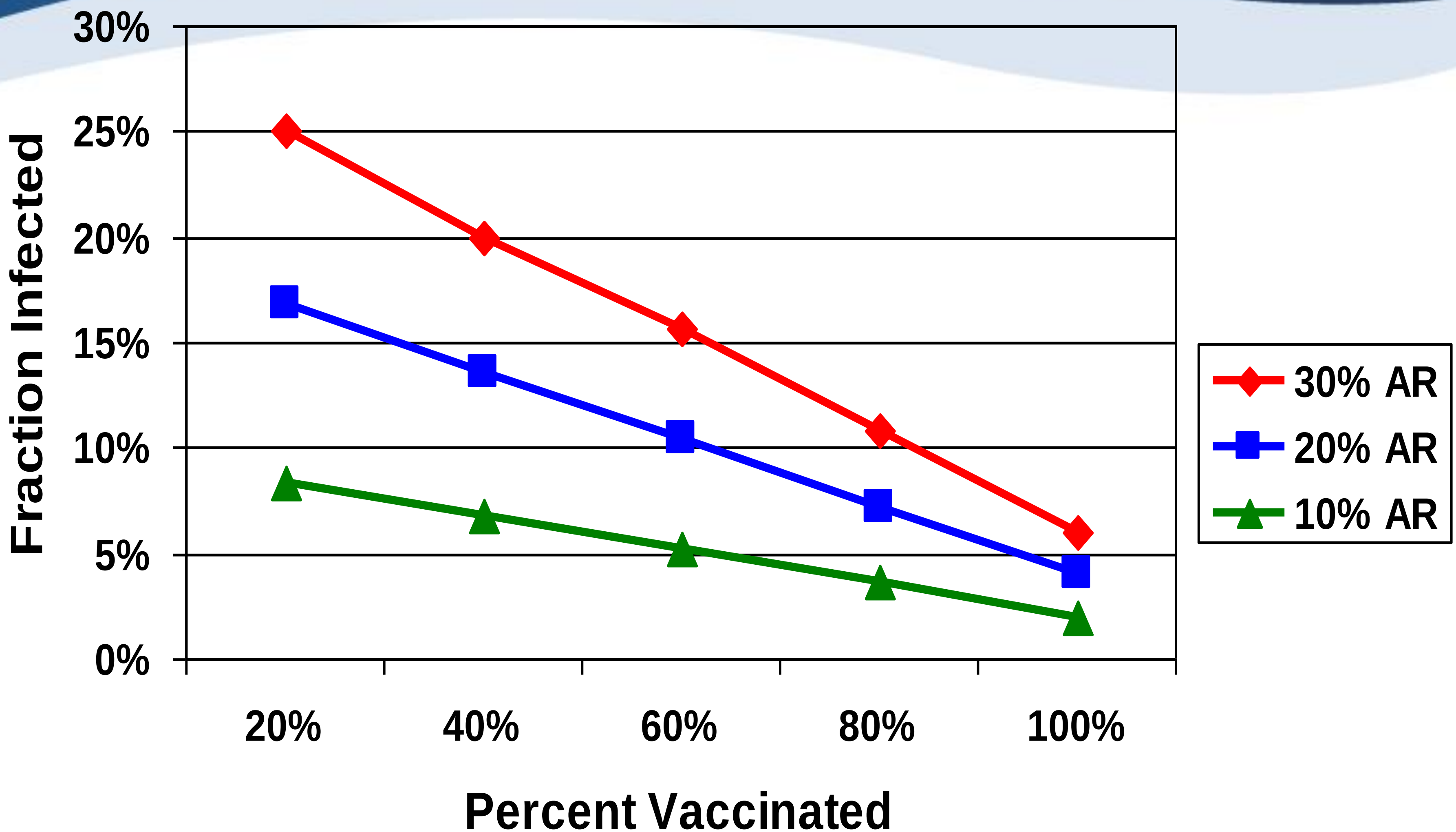
80% Vaccine Effectiveness
Effect of variable Attack (AR) and Vaccination Rates on the Proportion of the Population Infected



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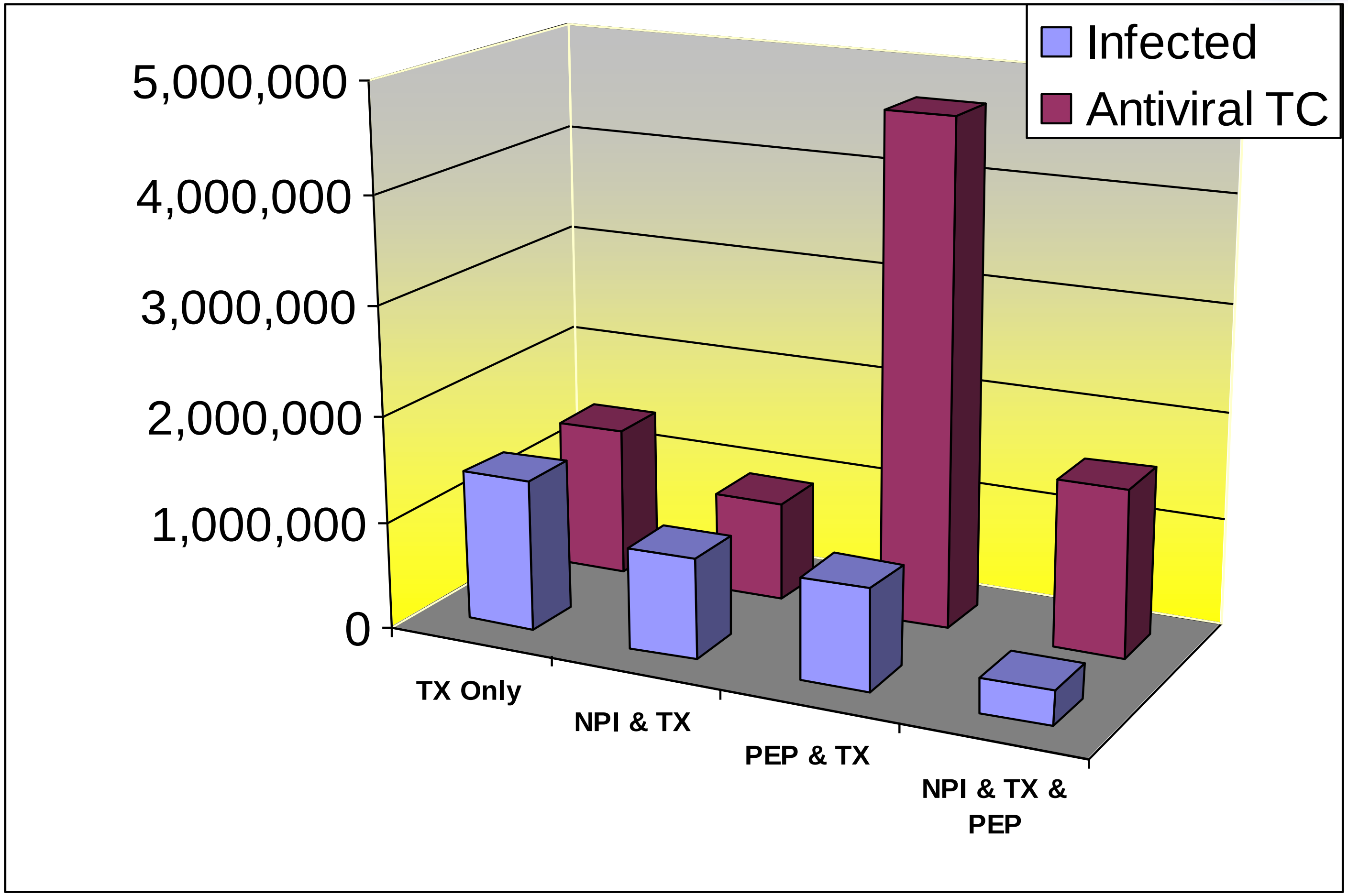
Antiviral Modeling

- Basic modeling using projected impact of a variety of strategies on DOD population
- Explored a number of existing models
- Used pre-existing modeling developed for Australia and applied DOD baseline data
- Universal findings:
  - Treatment alone will not halt the pandemic
  - Post exposure prophylaxis may blunt or halt the progression of a pandemic

Impact of Variable Antiviral Strategies on a population of 4.7 Million



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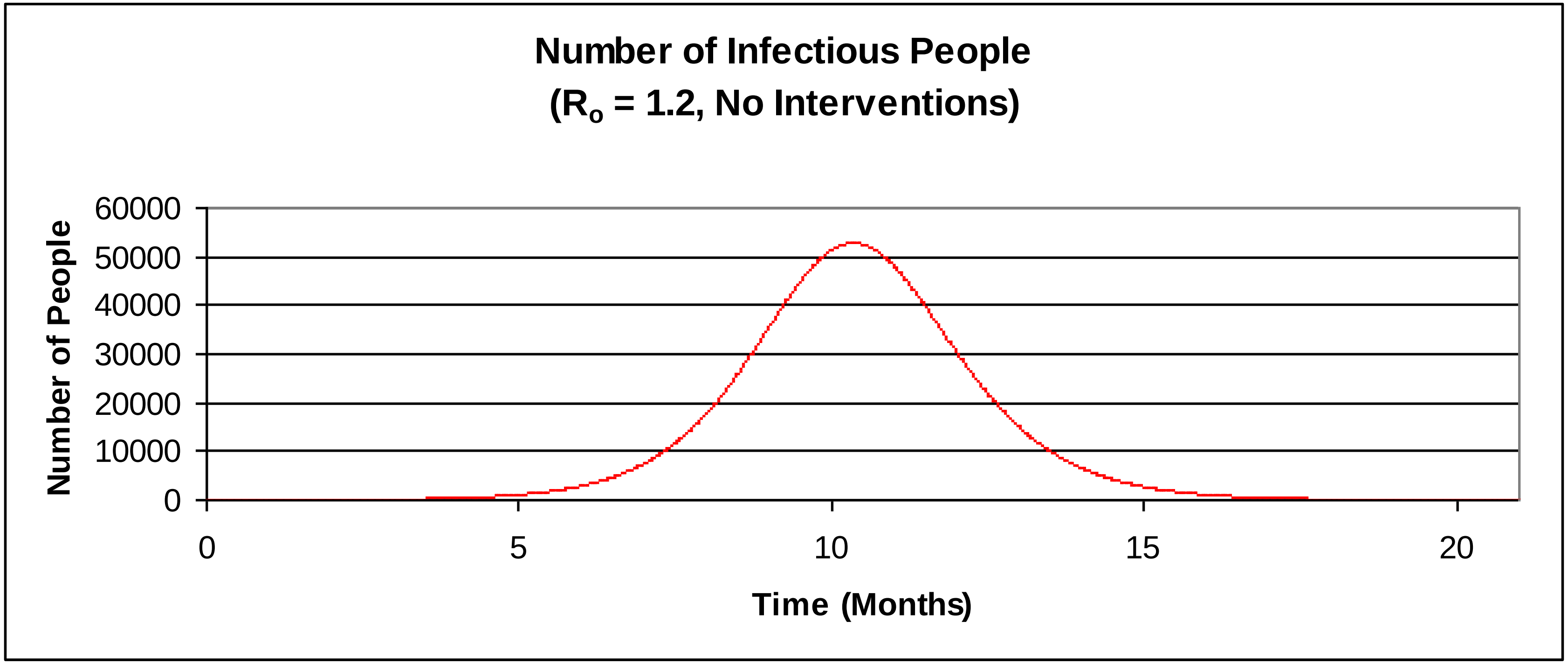
ANTIVIRAL REQUIREMENT BASED ON STRATEGY

	Requirement	# Infected	# of TC available for outbreak prophylaxis
PEP+TX+NPI	1,566,000	313,000	3,033,670
PEP + TX	4,700,000	940,000	Exhausts Stockpile
TX + NPI	940,000	940,000	3,600,000
TX	1,410,000	1,410,000	3,190,000

SEIR Modeling

- Used an existing model developed for the Australian Department of Health
- Population defined as
  - **S**usceptible
  - **E**xposed
  - **I**nfectious
  - **R**emoved (immune or dead)
- We added the variables of:
  - Population 4.7 Million
  - Variable infectivity (R_0 1.2 - 2.4)
  - 30, 50, 80% provided post exposure prophylaxis
  - 80% treatment of those infected

Unmitigated Pandemic R_0 1.2



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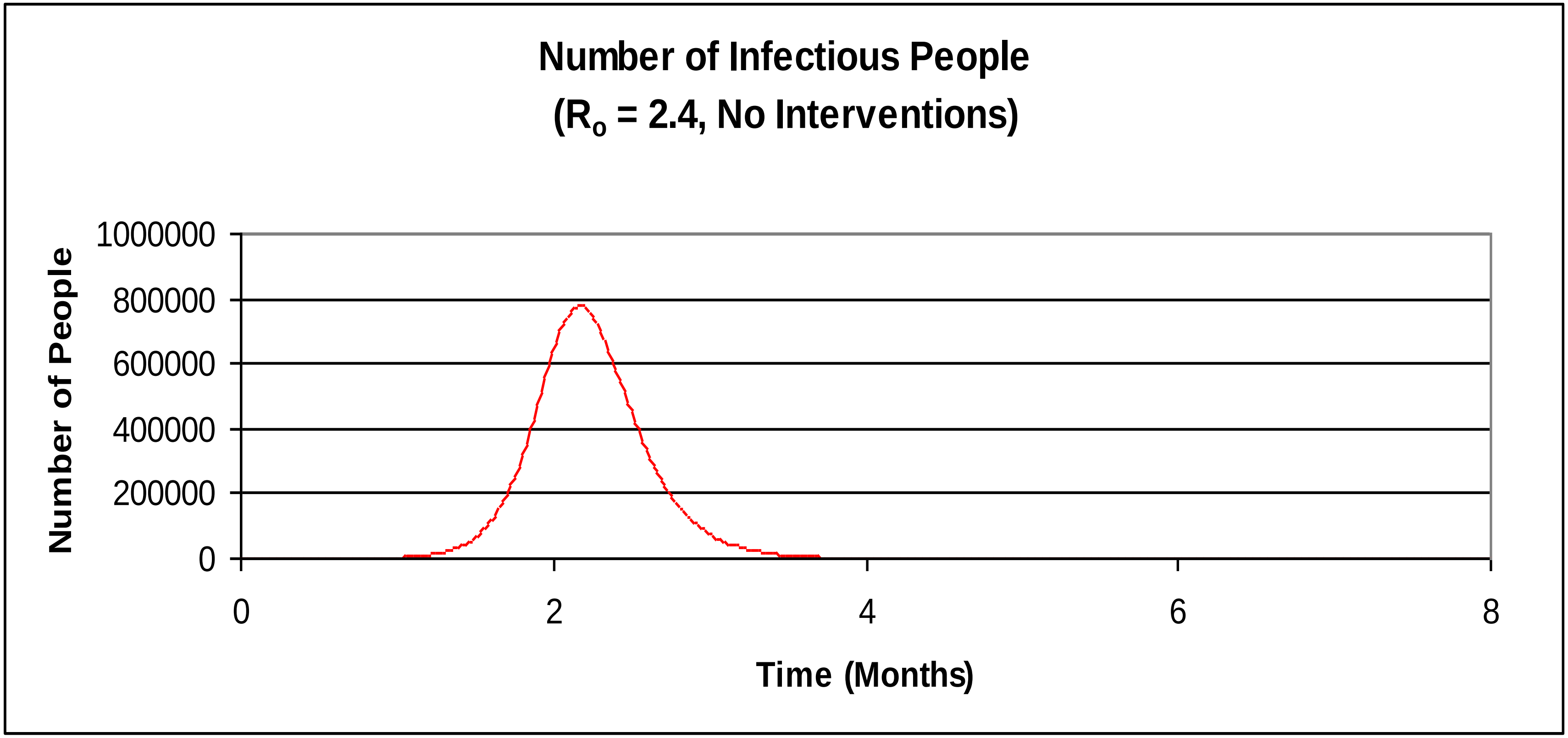
Unmitigated Pandemic R_0 2.4



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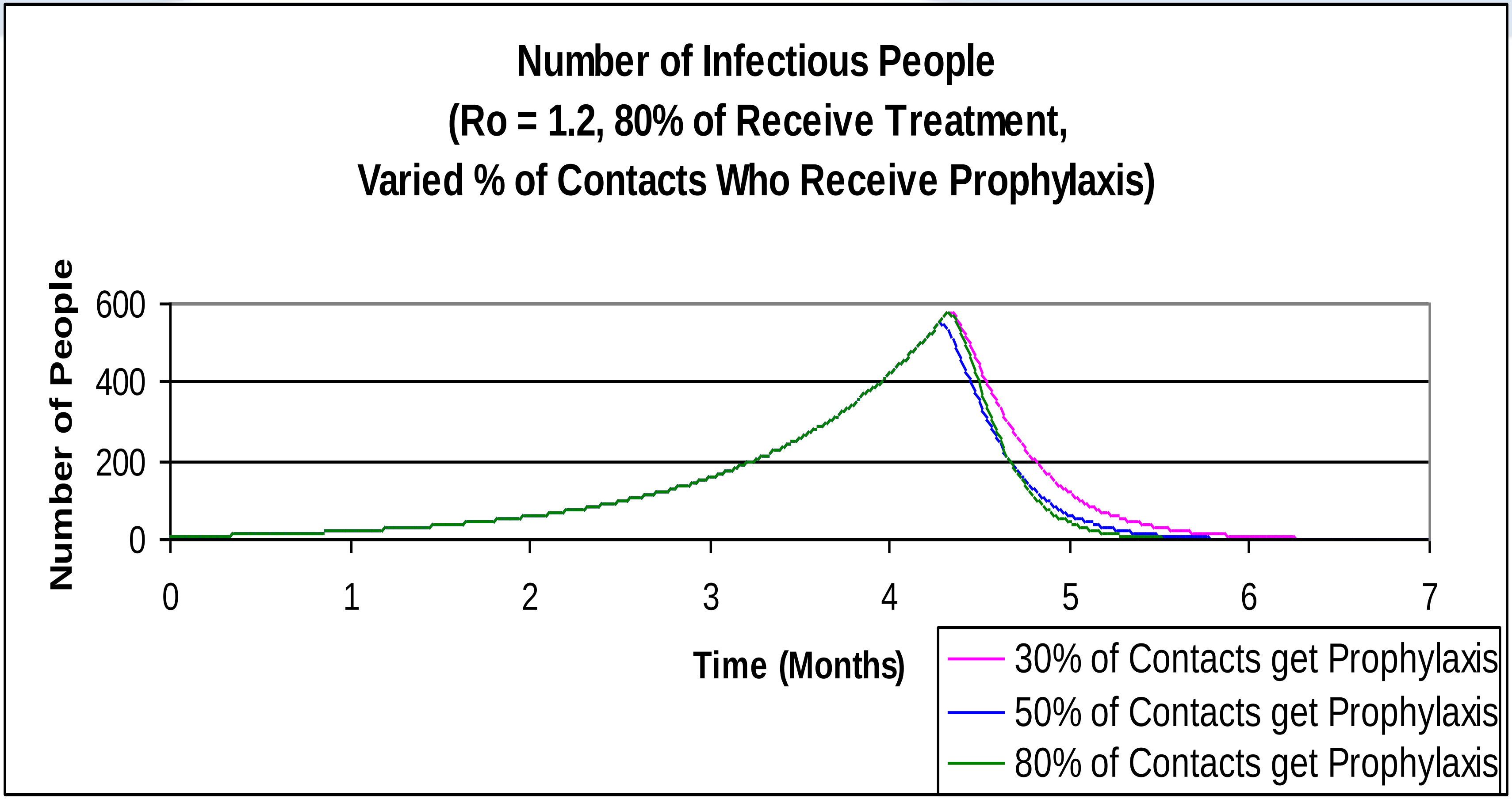
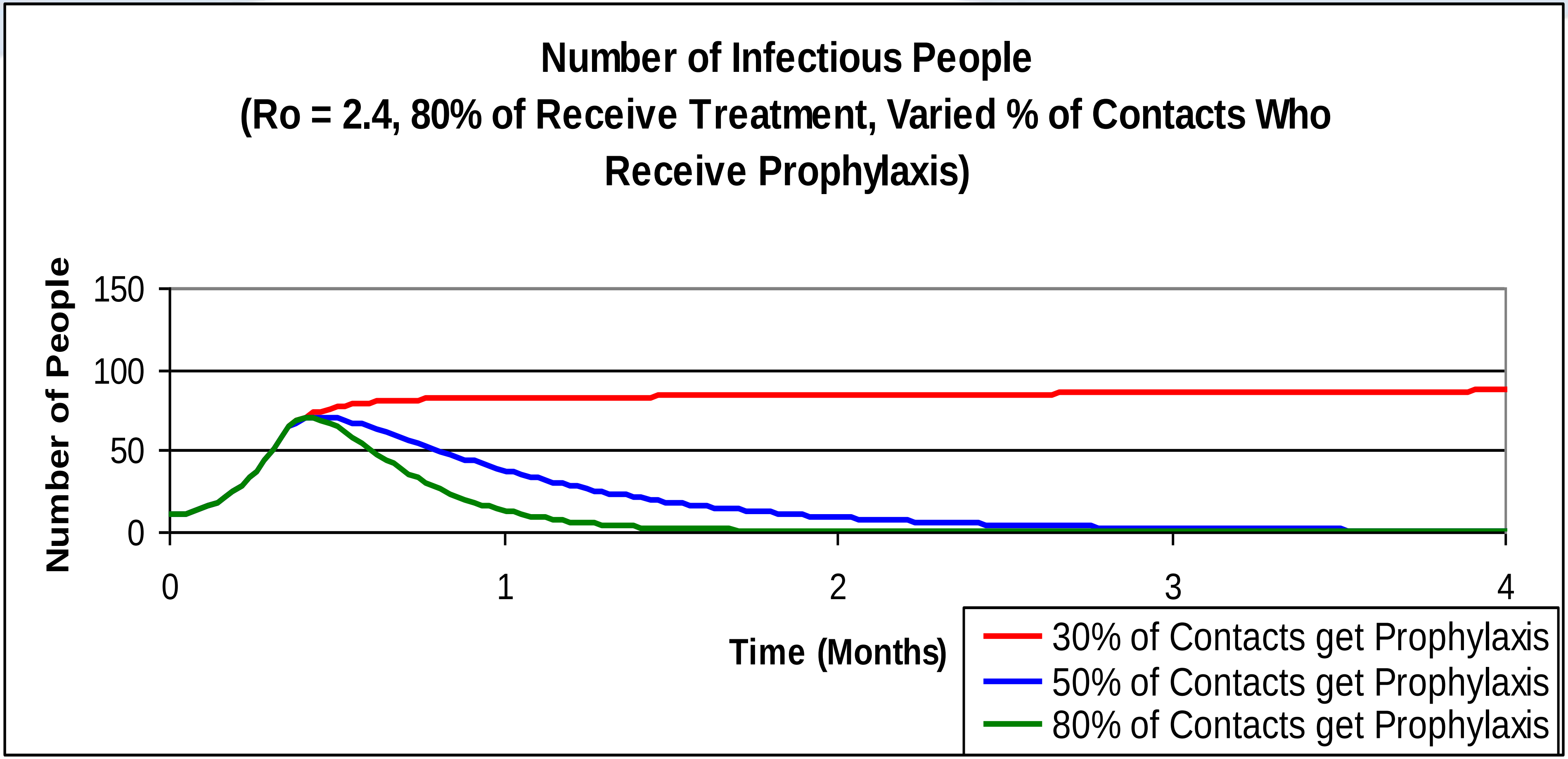
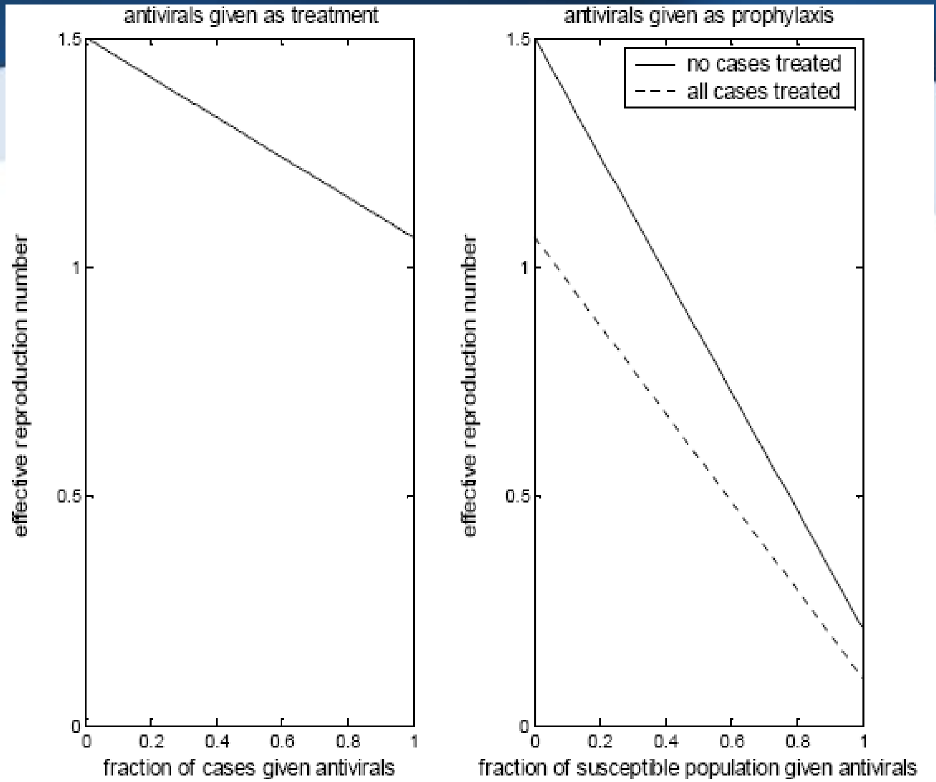
Effect of variable post exposure prophylaxis R_0 1.2



Effect of 80% treatment and variable post exposure prophylaxis R_0 2.4



- Do other models tell the same story
  - PEP stops the pandemic
  - PEP reduces hospitalizations
  - PEP has a synergistic effect with other measures

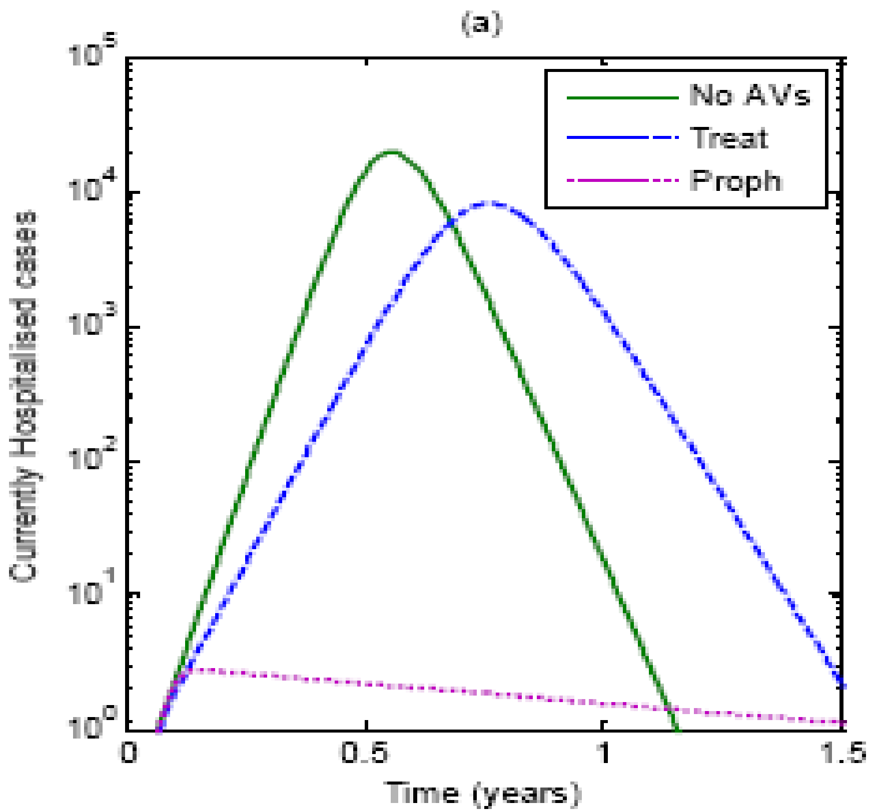


The effective reproduction number achieved by using antivirals for treatment and post exposure prophylaxis. Assumes a basic reproduction of 1.5 and that individuals are isolated 2 days after the development of symptoms.

Taken from: Becker NG et al. Using Mathematical Models to Assess Responses to an Outbreak of an Emerged Viral Respiratory Disease. The Australian National University, National Centre for Epidemiology and Population Health April 2006

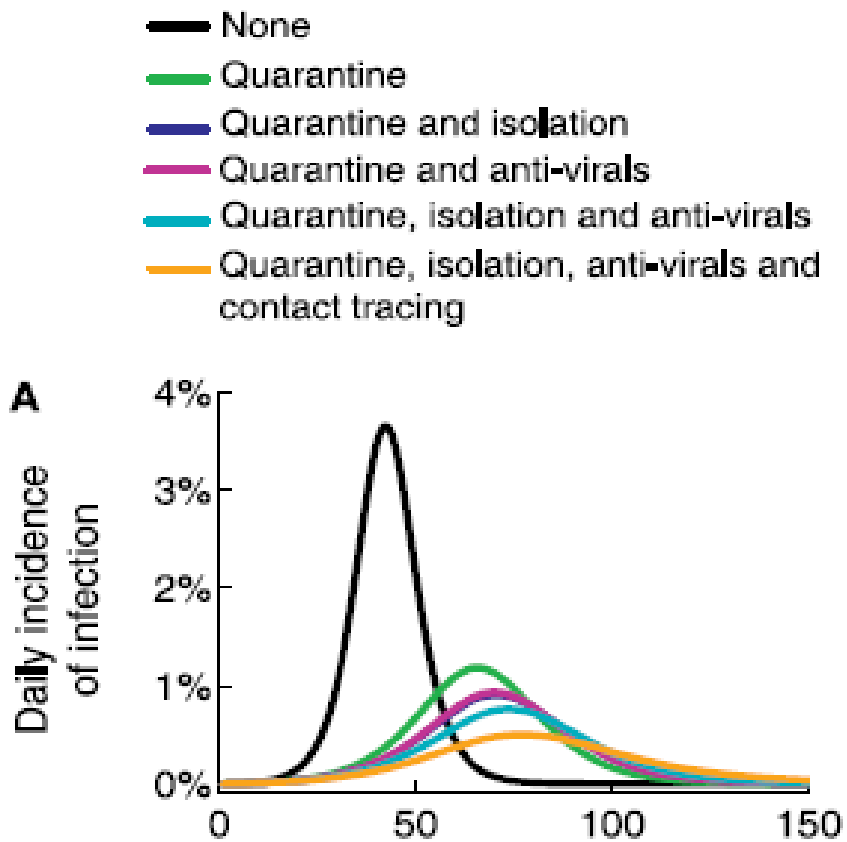
Cases in need of hospitalization over time from a baseline attack rate of 50% for three antiviral strategies

(no antivirals, treatment alone, post exposure prophylaxis)



Taken from Becker NG et al. Using Mathematical Models to Assess Responses to an Outbreak of an Emerged Viral Respiratory Disease.

Additive effect of various interventions on daily incidence of infection assuming a compliance rate of 50%.

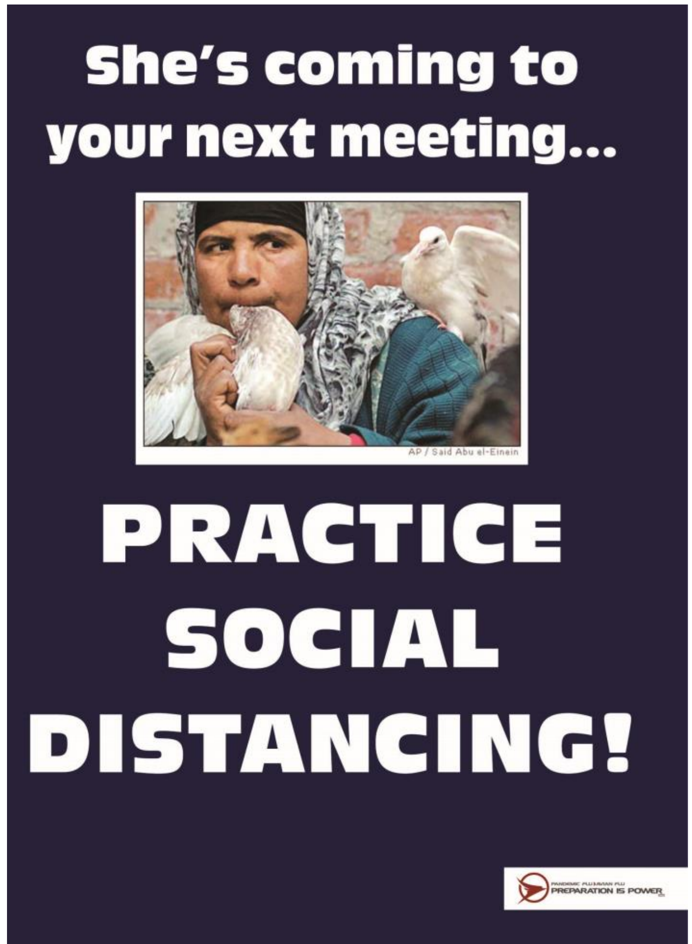


Wu JT, et al. PLoS Med 3(9);e361. March 31, 2006

Modeling Summary

- Unadjuvanted vaccine will have a modest impact on mitigation
- Adjuvanted or other more effective vaccines will have a substantial effect on pandemic mitigation
- Antiviral use limited to treatment will not result in substantial reductions in overall impact on the DOD community
- Addition of an antiviral post-exposure prophylaxis strategy, combined with infection control and social distancing measures may halt a pandemic

Questions?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