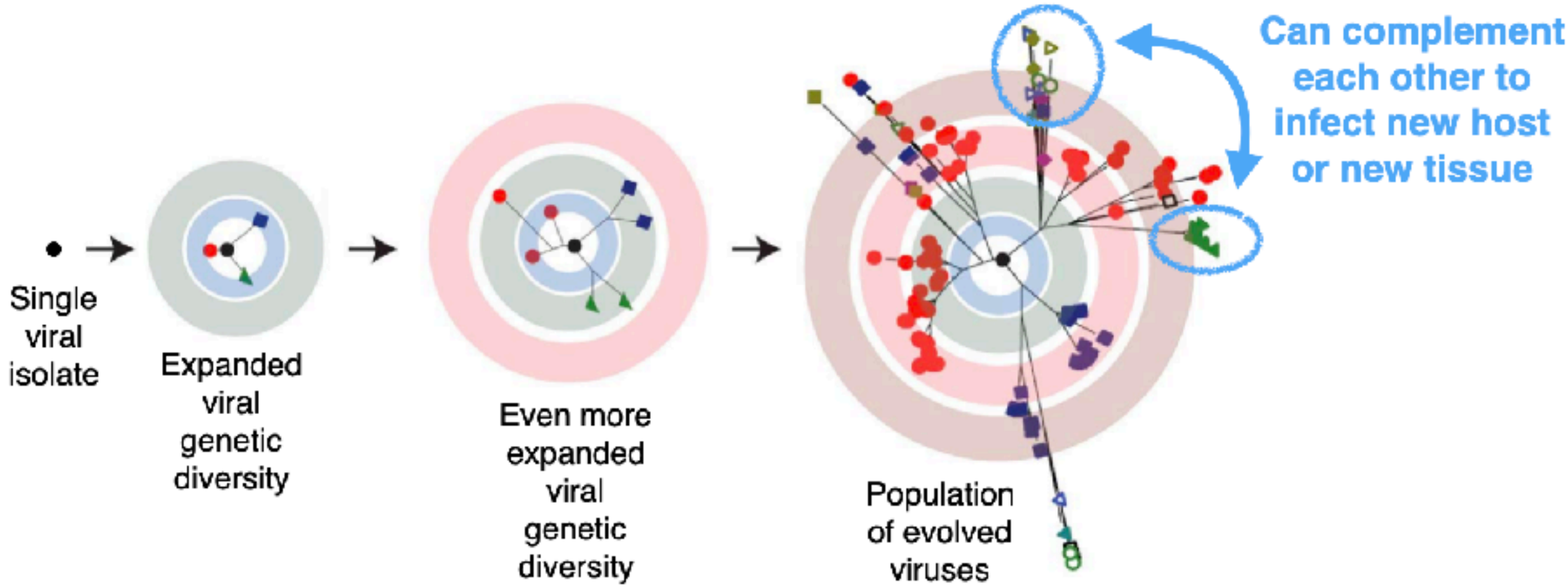
BIMM114: VIROLOGY



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Outline for today's lecture

Key concepts in this lecture:

Review of R_0 and R_{eff} and required vaccination calculations

Chance to ask questions about pre-recorded lecture

Vignuzzi et al., Nature, 2005

R_0 - THE BASIC REPRODUCTIVE NUMBER

One person is infected. How many more people will they infect in a naive group?

Called the "basic reproductive number" or R_0 (pronounced "R naught")

R_0 **=** **Number of contacts in a given time** **X** **Transmission probability per contact** **X** **Duration of infection**

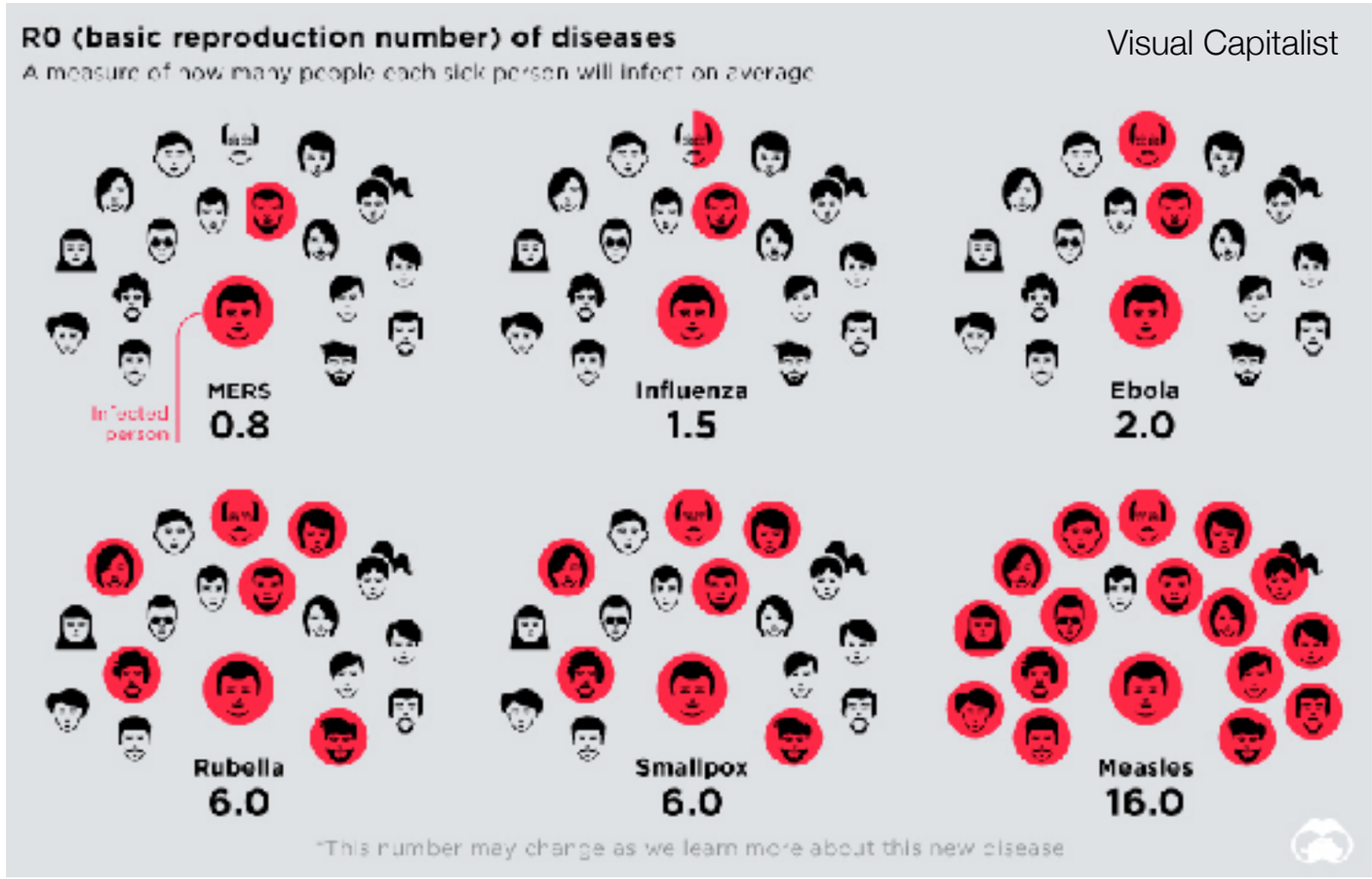
R_0 **> 1** Epidemic continues

R_0 **< 1** Epidemic dies out

R_0 - THE BASIC REPRODUCTIVE NUMBER

Estimates for some epidemic viruses:

- ***Measles***: 12-18
- ***Polio***: 5-7
- ***Influenza***: 1-3
- ***HIV***: 2-5
- ***Ebola (2013-2016)***: 1.5-2.5
- ***MERS***: <1
- ***SARS-CoV-2 (original)***: 2-3
- ***SARS-CoV-2 (variant)***: >5?

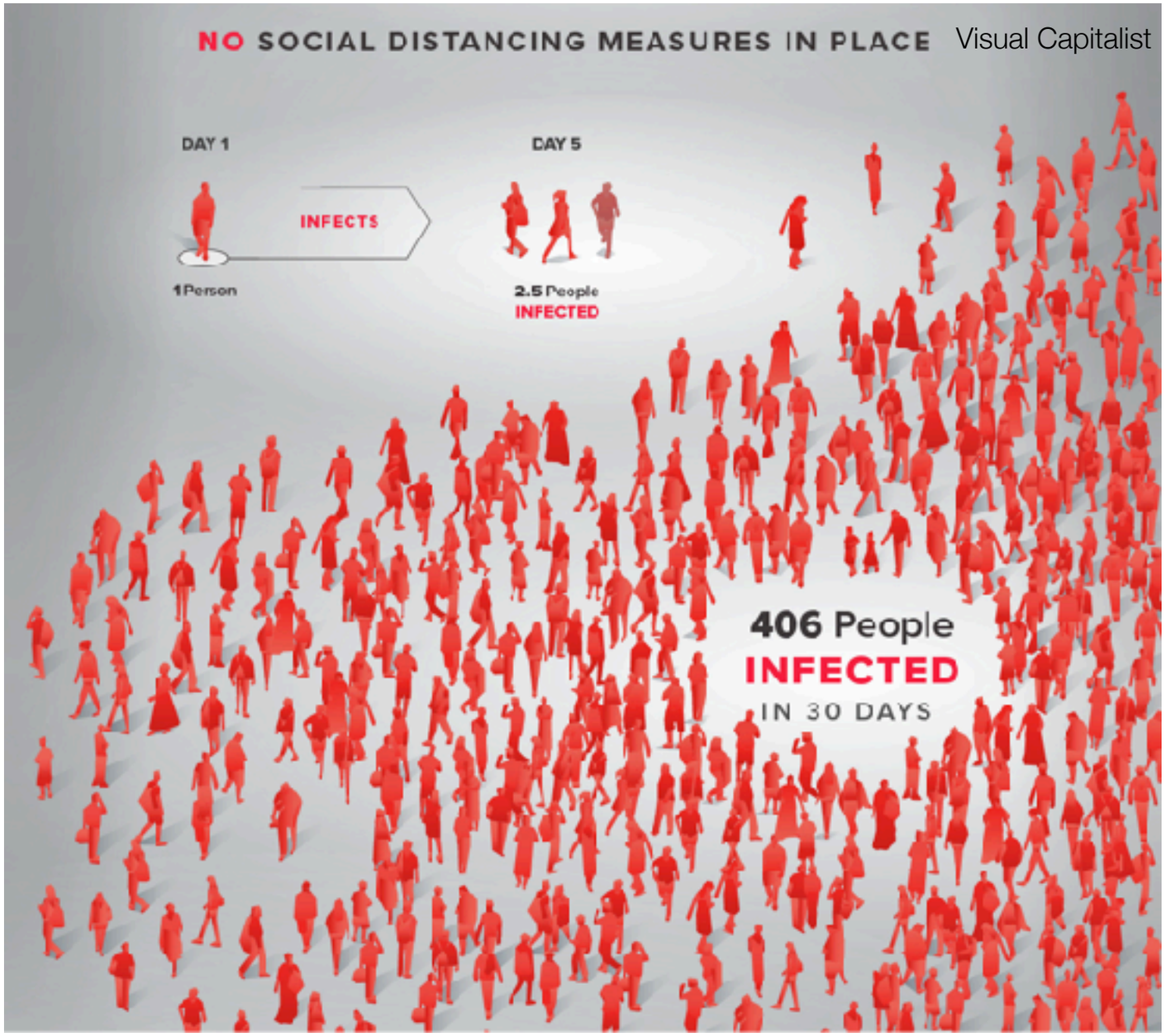


R_0 = Number of contacts in a given time X Transmission probability per contact X Duration of infection

What are two ways to reduce R_0?

SOCIAL DISTANCING, MASKING, ETC. REDUCE R_0

$$R_0 = \text{Number of contacts in a given time} \times \text{Transmission probability per contact} \times \text{Duration of infection}$$



Slide credit: Stephen Hedrick

EFFECTIVE R ACCOUNTS FOR HOST IMMUNITY

$$R_0 = \text{Number of contacts in a given time} \times \text{Transmission probability per contact} \times \text{Duration of infection}$$

$$\text{Effective } R = R_0 \times \text{Fraction of susceptible population}$$

This is the basis for herd immunity

Tells us how much of the population needs to have immunity to stop an outbreak

Let's assume measles virus has an R_0 of 10, what % of the population needs to be immune to prevent an outbreak?

R_{EFF} AND VACCINATION RATE QUESTIONS

A virus has an R_0 of 2. What percentage of the population needs to have immunity to stop an outbreak?

A virus has an R_0 of 2. There is no natural immunity, but we have a vaccine that works pretty well. Every person that gets the vaccine has a 66.6% chance of gaining immunity to the virus. What percentage of the population needs to receive the vaccine to stop an outbreak?

In the above scenario, if the population is 100 million people, how many vaccine doses do we need to stop the outbreak?

A different virus has an R_0 of 10. What percentage of the population needs to have immunity to stop an outbreak?

In this case, we have a better vaccine that provides immunity 80% of the time. Can we stop the outbreak using this vaccine alone?

Outline for today's lecture

Key concepts in this lecture:

Review of R_0 and R_{eff} and required vaccination calculations

Chance to ask questions about pre-recorded lecture

Vignuzzi et al., Nature, 2005

Questions on the pre-recorded lecture?

Vignuzzi et al., Nature, 2006

Some questions to focus on for the paper discussion

What is the main question the paper is trying to address?

What was known before this paper?

What is the hypothesis of the study?

What are the primary experimental approaches?

What are the main conclusions?

Are the conclusions supported by the data?

Are there any caveats about the paper?

What are the next steps?

Why am I having you read this paper?

Why is this paper important for the field of virology?

RATIONALE FOR STUDY?

Quasispecies diversity determines pathogenesis through cooperative interactions in a viral population

What is the main question the paper is addressing?

What was known before this paper?

What is the hypothesis of the study?

Do you think they really went in with this question or they constructed this after they saw the data?

An RNA virus population does not consist of a single genotype; rather, it is an ensemble of related sequences, termed quasispecies[1–4]. Quasispecies arise from rapid genomic evolution powered by the high mutation rate of RNA viral replication[5–8]. Although a high mutation rate is dangerous for a virus because it results in nonviable individuals, it has been hypothesized that high mutation rates create a 'cloud' of potentially beneficial mutations at the population level, which afford the viral quasispecies a greater probability to evolve and adapt to new environments and challenges during infection[4,9–11]. Mathematical models predict that viral quasispecies are not simply a collection of diverse mutants but a group of interactive variants, which together contribute to the characteristics of the population[4,12]. According to this view, viral populations, rather than individual variants, are the target of evolutionary selection[4,12]. Here we test this hypothesis by examining the consequences of limiting genomic diversity on viral populations. We find that poliovirus carrying a high-fidelity polymerase replicates at wild-type levels but generates less genomic diversity and is unable to adapt to adverse growth conditions. In infected animals, the reduced viral diversity leads to loss of neurotropism and an attenuated pathogenic phenotype. Notably, using chemical mutagenesis to expand quasispecies diversity of the high-fidelity virus before infection restores neurotropism and pathogenesis. Analysis of viruses isolated from brain provides direct evidence for complementation between members in the quasispecies, indicating that selection indeed occurs at the population level rather than on individual variants. Our study provides direct evidence for a fundamental prediction of the quasispecies theory and establishes a link between mutation rate, population dynamics and pathogenesis.

TABLE 1

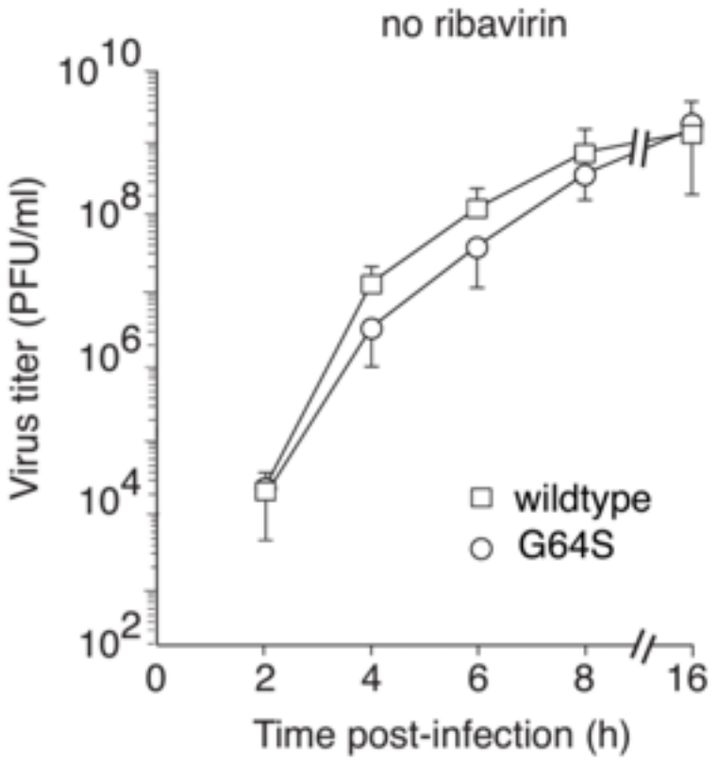
Table 1 | Genomic diversity for wild-type, G64S and G64S^{eQS} populations

Virus	Total number of mutations*	Mutations per genome	gua^r variants†
Wild type	13/50,700	1.91	62 ± 6
G64S	2/50,700	0.31	22 ± 8
G64S^{eQS}	14/50,700	2.06	56 ± 6
Wild type^b‡	12/48,588	1.84	ND
G64S^b‡	6/69,000	0.65	ND
G64S$^{eQS\text{-}b}$‡	6/50,700	0.88	ND

*Number of mutations observed over the total number of nucleotides sequenced. To determine the mutation frequency in each poliovirus population, 24 independent poliovirus cDNA clones were obtained. Poliovirus cDNAs were generated by RT–PCR from viral RNA isolated from single plaques in a standard plaque assay. A significant difference in the number of mutations was observed between wild-type and G64S viruses ($P < 0.002$, Mann-Whitney U-test). In contrast, no significant difference was observed between wild-type and G64S^{eQS} viruses ($P < 0.222$).

†Per 10^6 plaque-forming units (p.f.u.), mean ± s.d. of six experiments. Significance testing yielded $P < 0.001$ by analysis of variance (ANOVA).

‡Wild-type^b, G64S^b and G64S$^{eQS\text{-}b}$ viruses re-isolated from infected brain. Number of gua^r variants was not determined (ND).



What are these data showing?

What is G64S?

What is one important control in comparing these viruses?

What is G64S^{eQS}?

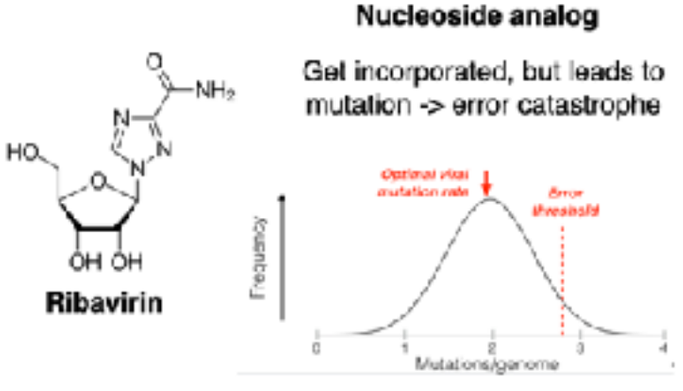
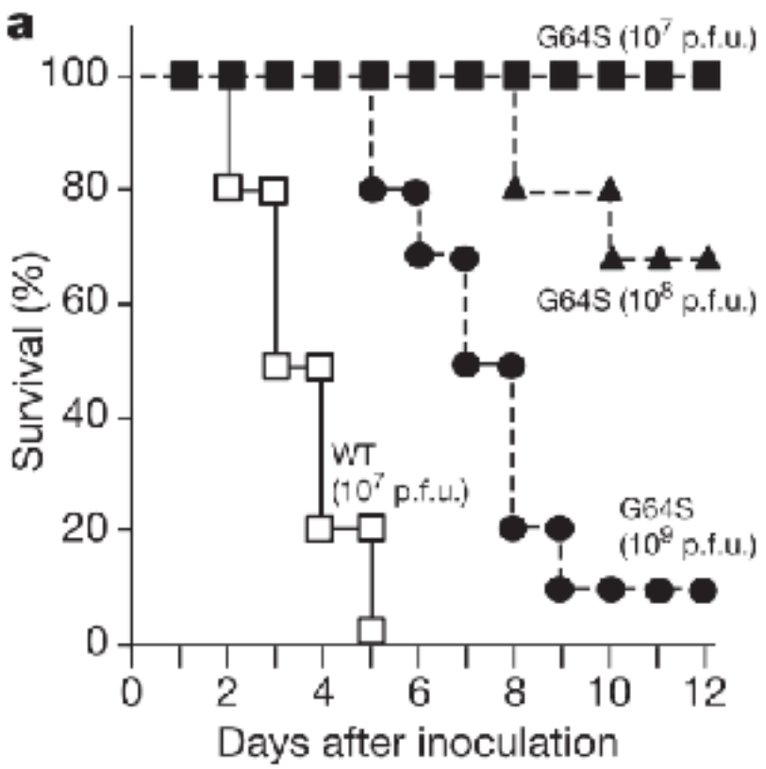


FIGURE 1



What are these data showing?

How are these experiments done?

c

Virus	LD_{50} (p.f.u.)
Wild type	1.2×10^6
G64S	3.9×10^8
$G64S^{eGS}$	1.7×10^6

What is the conclusion of this table?

FIGURE 2

What was their next question?

How are these experiments done?

What are the conclusions?

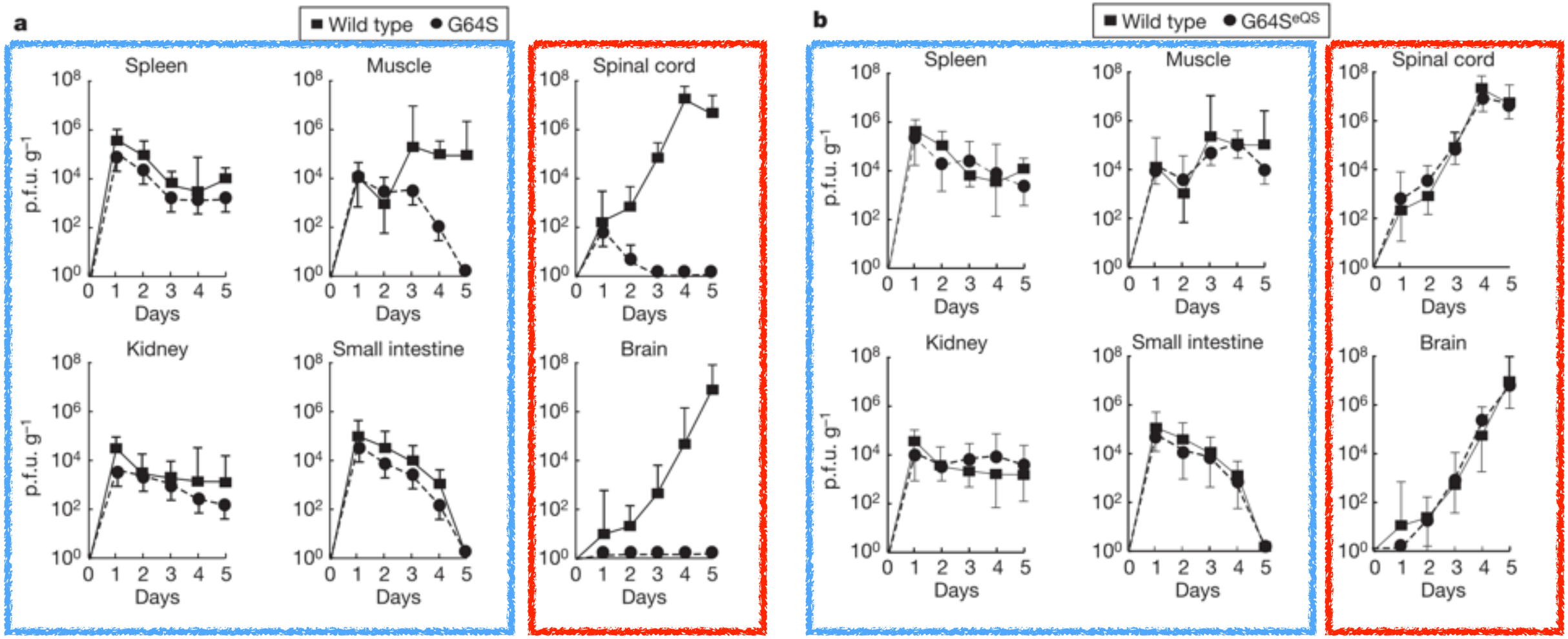


FIGURE 3A

What is the most simple explanation for their previous data (increasing viral diversity increases neuropathogenesis)?

What in Figure 3a says that's not the explanation?

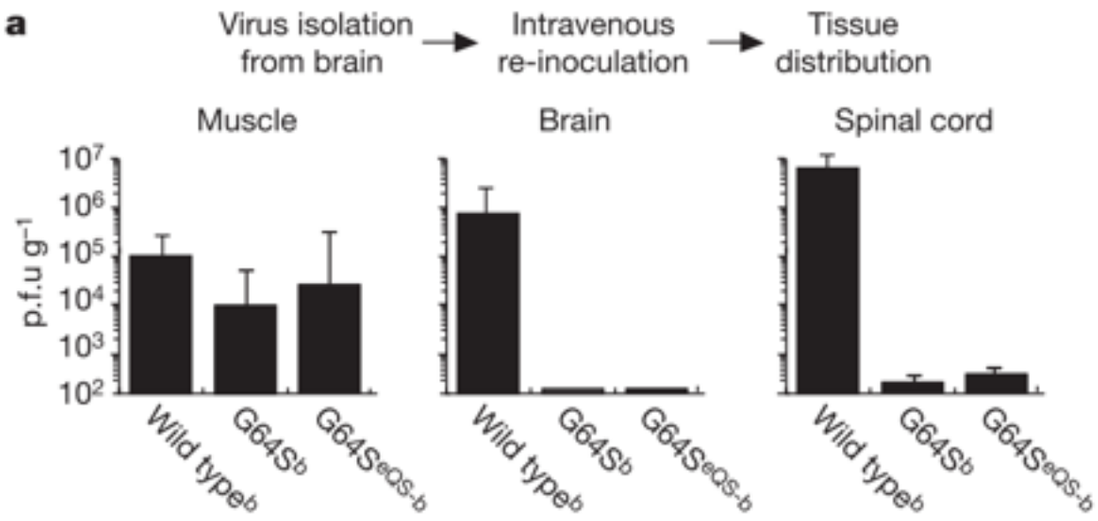


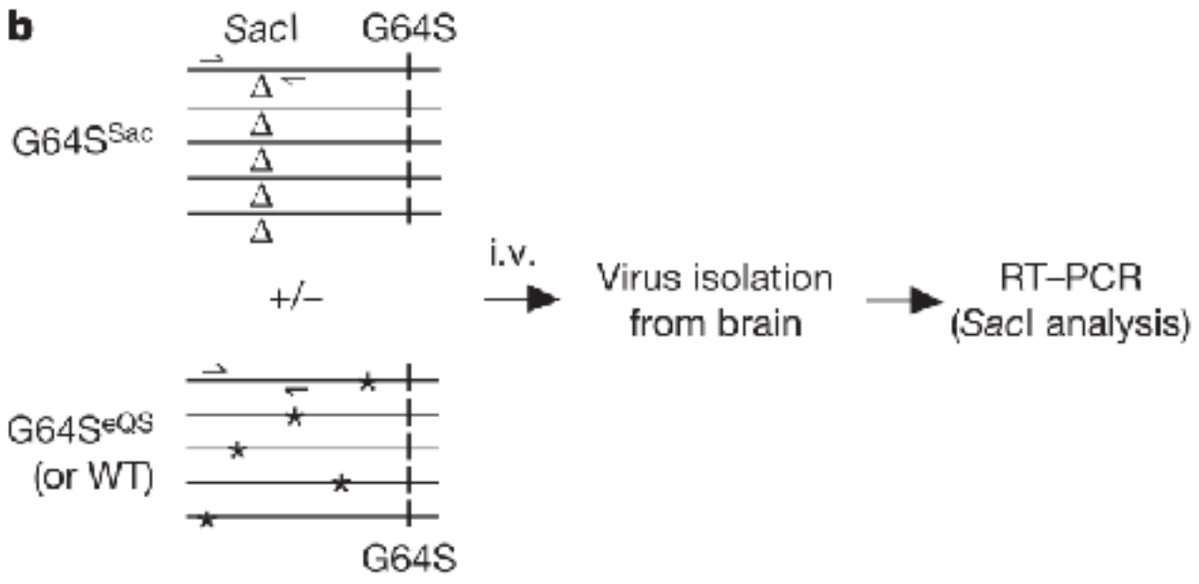
FIGURE 3B-C

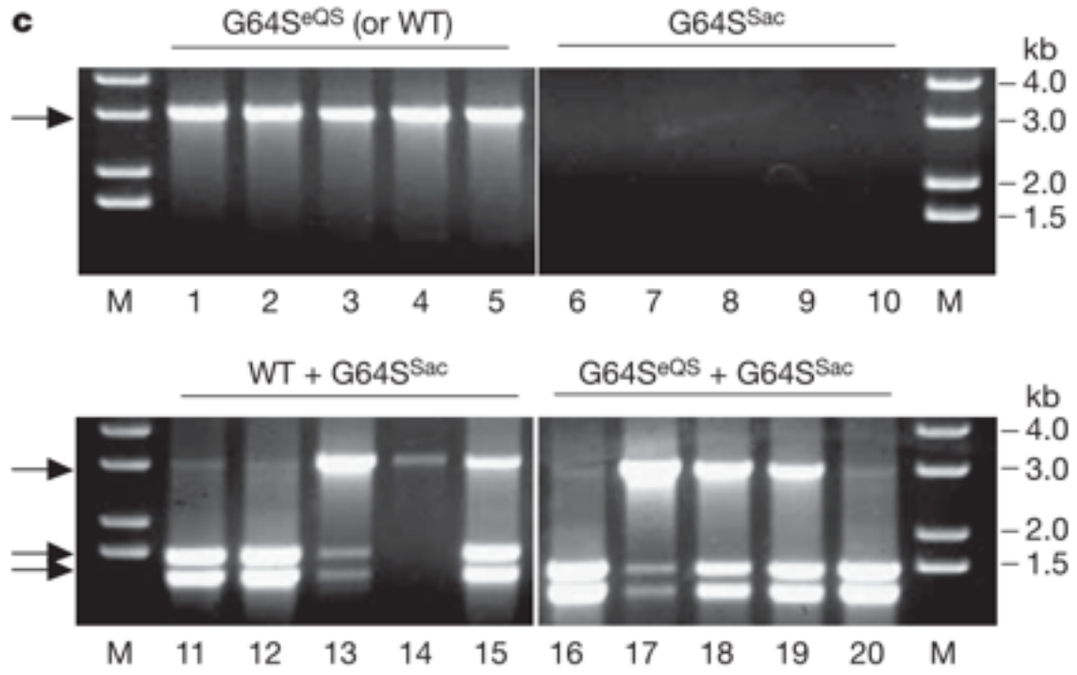
What is another explanation for the observation that increasing viral diversity increases neuropathogenesis?

How do they test that?

What do the data say?

What is their conclusion?





CONCLUSIONS/CAVEATS/IMPACT

What were the main conclusions?

Are the conclusions supported by the data?

Are there any caveats about the paper?

What are the next steps?

> Nat Med. 2008 Feb;14(2):154-61. doi: 10.1038/nm1726. Epub 2008 Feb 3.

Engineering attenuated virus vaccines by controlling replication fidelity

Marco Vignuzzi [1], Emily Wendt, Raul Andino

Why did I have you read this paper?

Why is this paper important for the field of virology?

QUESTIONS?

Next week

Tuesday and Thursday will be guest lectures from Dr. Dustin Glasner, expert in Flaviviruses and viral pathogenesis

Tuesday: Flaviviridae and Togaviridae

Thursday: Viral pathogenesis

For Tuesday (2/6) read the assigned reading in textbook:

Chapter 12 & 13

For Thursday, there are no pre-class readings

We hope to have midterms graded by next Tuesday, but certainly by next Thursday