Accelerating vaccine innovation for emerging infectious diseases via parallel discovery

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NBER EIPE Conference
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The Business of Vaccines

- Business model for vaccines is challenging
- Non-profits like CEPI, WHO, CARB-X, Gates Foundation are helping
- But philanthropy is not enough
- Is it possible to attract more private-sector investment to address emerging infections diseases?

Investment Pop Quiz #1

$$\text{Sharpe Ratio} \equiv \frac{\mathrm{E}[R] - R_f}{\mathrm{SD}[R]}$$

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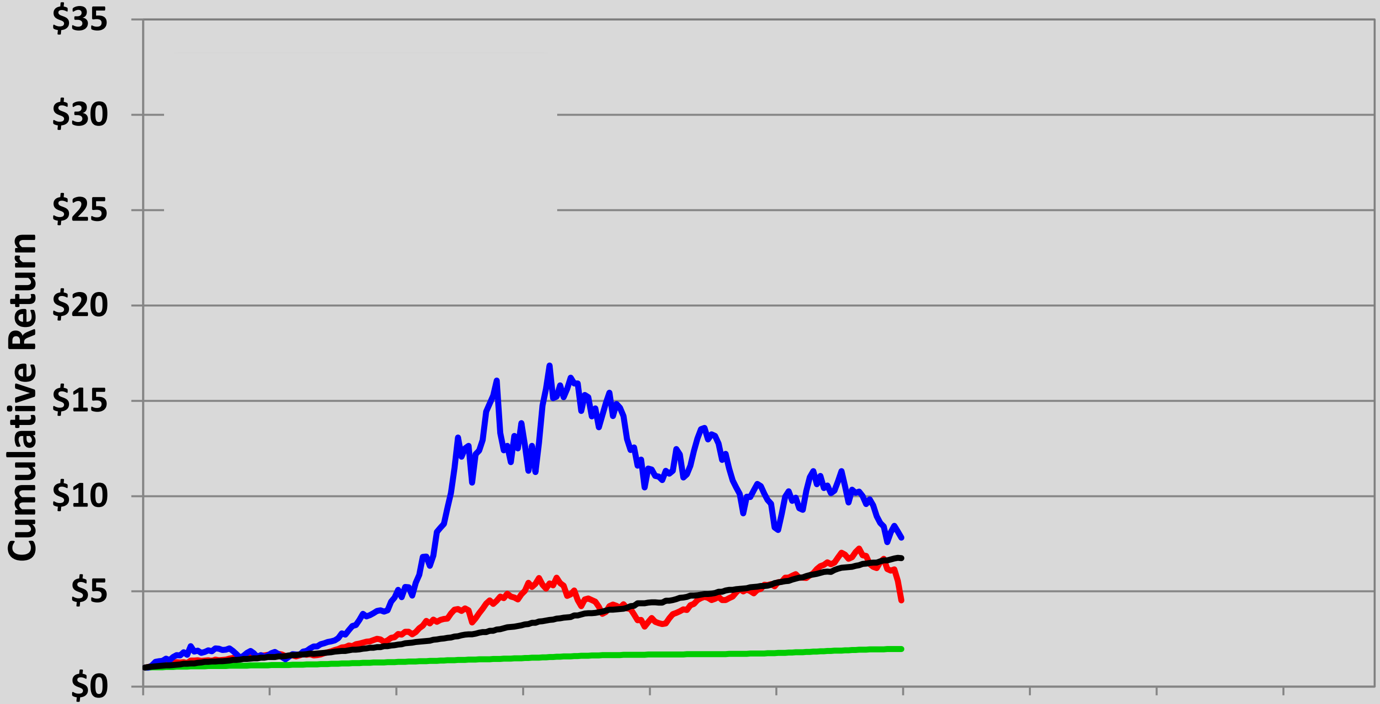


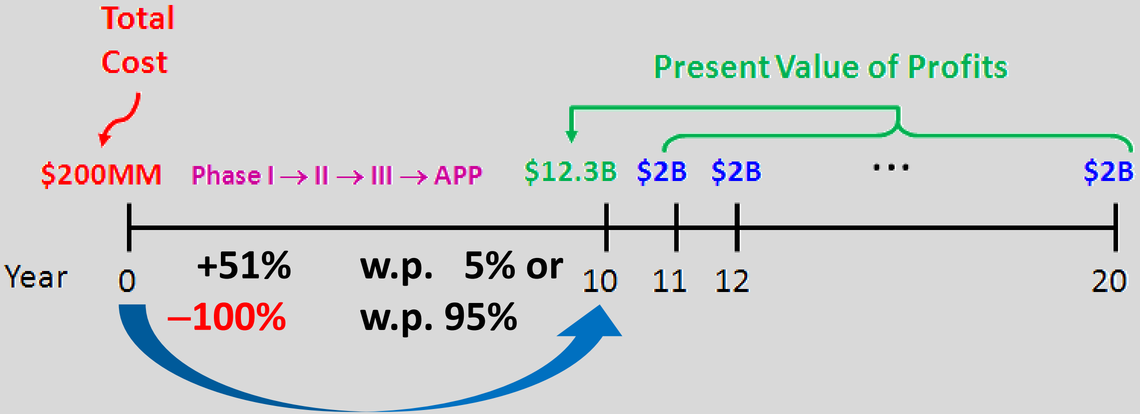
3 May 2022

Investment Pop Quiz #2

Would You Invest In This Project?

E[R] = 11.9%
SD[R] = 423.5%
SR = 0.03

- $200MM investment, 10-year horizon
- Probability of positive payoff is 5%
- If successful, annual profits of $2B for 10 years



Financial Engineering Can Help

What If We Invest In 150 Programs Simultaneously?:

- Requires \$30B of capital
- Assume programs are IID (can be relaxed)
- Diversification changes the economics of the business:

$$\mathrm{E}[R] = 11.9\%$$

$$\mathrm{SD}[R] = 423.5\% / \sqrt{150} = 34.6\% \Rightarrow \textbf{SR = 0.33}$$

- But can we really raise \$30B??
- It depends on the portfolio's risk/reward profile (correlations?)

Challenges of Vaccine Development

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Why did big pharma leave vaccine development (before the COVID-19 pandemic)?

Plotkin et al. (2015):

- Declining and highly uncertain **revenues**
- Lack of **funding** in the absence of an imminent threat
- Vaccines for uncommon but deadly infectious diseases are not as **profitable** as the seasonal flu

Challenges of Vaccine Development

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How has the pandemic changed vaccine development?

- **Innovations** in biomedical technology (e.g., mRNA vaccines)
- Unprecedented acceleration for **clinical development**
- Unprecedented **collaboration** among stakeholders
- Increased **public awareness** of the importance to prevent future pandemic outbreaks of emerging infectious diseases (EID)

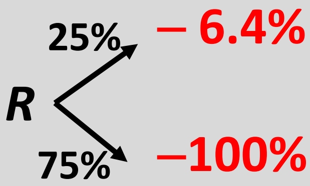
Investment Pop Quiz #3

Would You Invest In This Project?

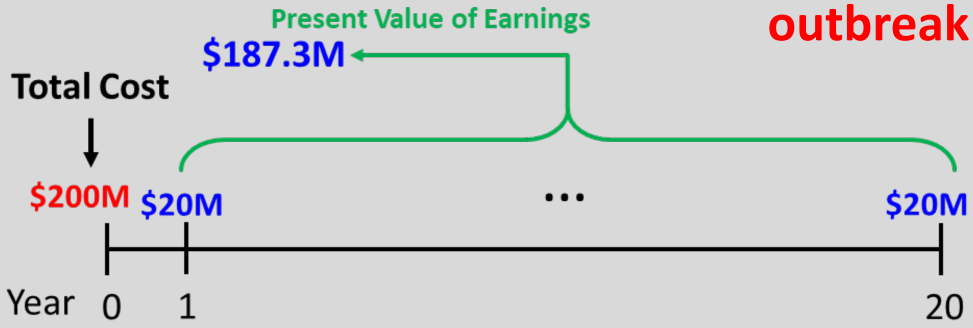
- $200M investment, 1-year horizon
- Probability of success is 25%
- If successful, $187.3M = PV_{20}(10% × $20/dose × 10M)

price doses

prob. of outbreak



SR = ???



Simulating a Vaccine Fund

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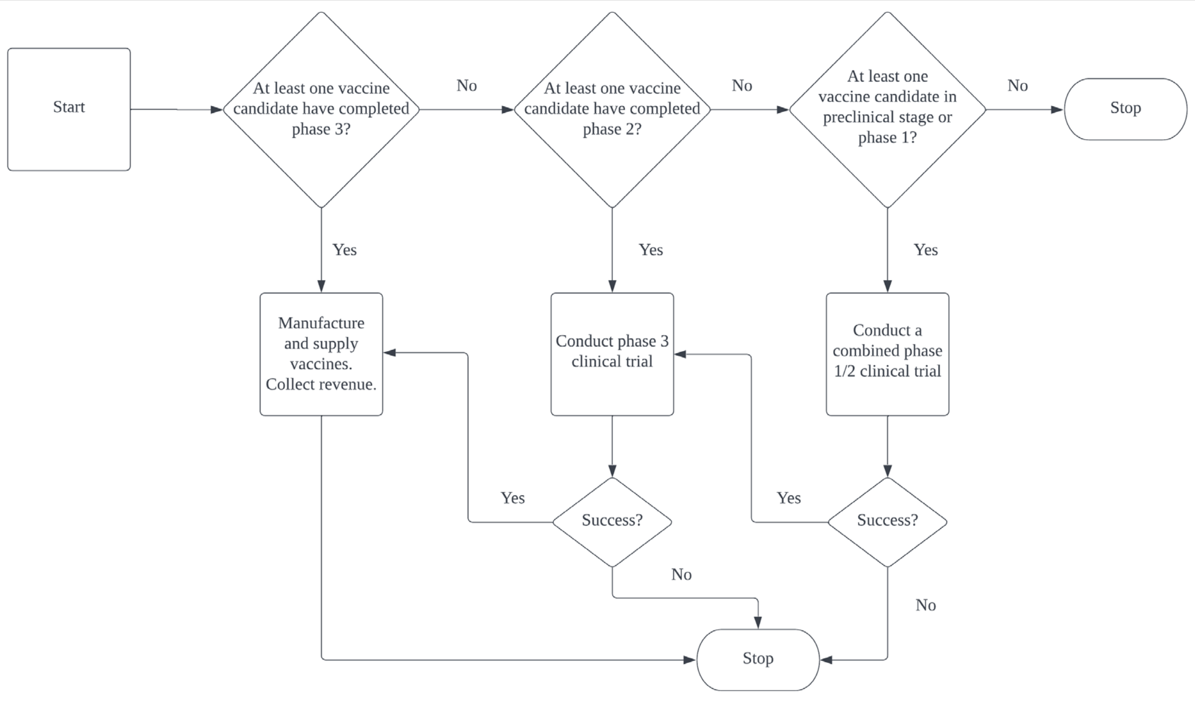
Disease	# Vaccine Candidates	Annual Probability of Outbreak (%)
Disease X	10	1.0
Chikungunya	16	10.8
Zika Virus	18	4.3
Lassa Fever	7	100.0
Rift Valley Fever	3	10.5
SARS-CoV-1	2	7.1
West Nile Virus	23	10.0
MERS-CoV	8	40.0
Crimean-Congo Hemorraghic Fever	7	12.5
Nipah Virus	20	15.8
Marburg Virus	6	12.0

- Adapted from CEPI and Vu et al. (2022)
- 10 vaccine candidates for “disease X” (pandemic)
- Simulate outbreaks over 20 years

Simulating a Vaccine Fund



- Simulate epidemics each year
- For each occurrence, follow flowchart

Simulating a Vaccine Fund

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Category	Item	Unit Cost (USD)	Quantity
Fixed cost	Production line	$58M	1 bioreactor of 30L working volume
Variable costs	Raw materials	$456.6M/(year · production line)	29,162 grams of mRNA per production line per year
	Consumables	$150M/(year · production line)	
	Labor	$20/hour	113,186 labor hours per production line per year
	Quality control	$10/hour	
	Fill-and-finish	$0.27/dose	10-dose vials
	Lab, utility, waste management, etc.	<1% total cost	Not modeled here

Sources: Kis & Rizvi (2021), Kis et al. (2021)

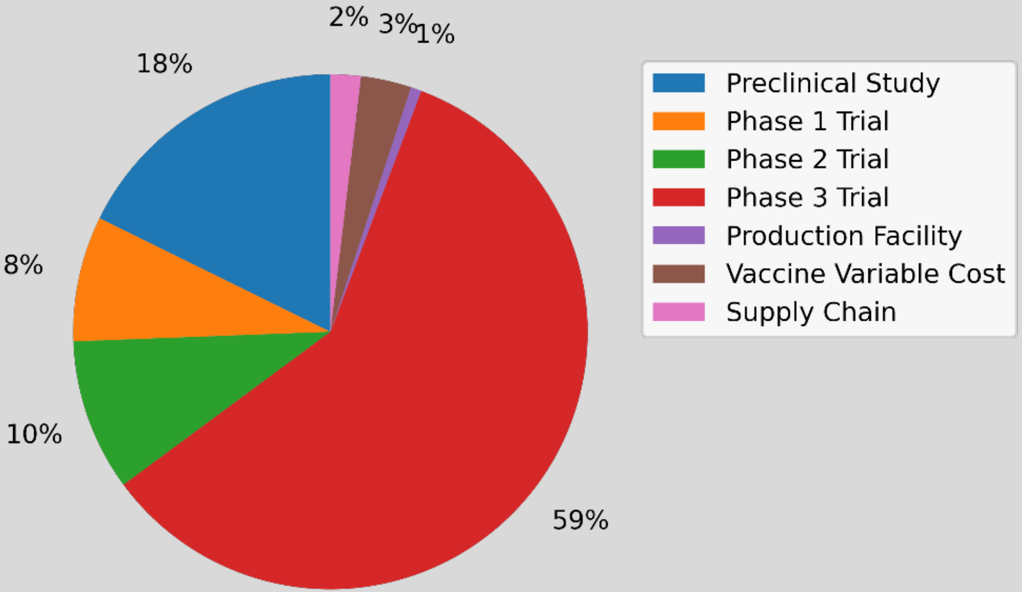
Results

Metric	Mean	Std Dev	Median
Annualized Return (%)	−6.0	6.7	−5.7
NPV ($ billion)	−9.5	4.1	−9.9
Investment ($ billion)	17.7	5.3	17.8
Revenue ($ billion)	7.5	7.7	5.8
Profit ($ billion)	−10.0	7.4	−11.5
# Epidemics Prevented	31	13	34

- Needs $9.5 billion to break even
- Prevents 31 epidemic outbreaks on average in the next 2 decades

Results

Costs of Vaccine Development and Delivery



- 94% of costs are clinical trials (59% in Phase 3)
- mRNA technology does not save much in costs (but reduces time!)

Sensitivity Analysis: Price

- Expected annual return is **negative** unless price per dose > $69.00
- Expected NPV is **negative** unless the price per dose > $78.00
- 12 common adult vaccines have list prices above $100.00 in US*

Price Per Dose	E[R_a]	SD[R_a]	E[NPV] ($B)	SD[NPV] ($B)
$20.00 (baseline)	−6.0%	6.7%	−9.5	4.1
$69.00	0.0%	7.1%	−1.4	11.9
$78.00	0.7%	7.1%	0.0	13.5
$100.00	1.9%	7.2%	3.6	17.4

*US CDC (Jan. 1, 2022)

What Can Be Done?

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- Pricing policy innovation:
  - AMCs, subscription model, etc.
- More generally, government policy is key
- Is healthcare a privilege or a right? Ethics?
- Should vaccine and anti-infective companies be considered "regulated utilities"?
- Finance can play a **positive** role in facilitating public health

What Can Be Done?

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Government involvement is essential when:

1. The investment **horizon** is long (over a decade)
2. The **capital** required is significant (~ $200 million)
3. The **probability of success** is low (~ 25% overall)
4. Potential **benefits** to the society are large

"Long Shot"
Hull, Lo, Stein
(2019)

$$\text{Sharpe Ratio} = \frac{\text{Private–Sector Reward}\uparrow}{\text{Risk}\downarrow}$$

- Risk-based "market failure" (Lo, 2022)

Thank You!

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Supplementary Materials

Simulating a Vaccine Fund

- Probability of success (PoS)
- Correlation of trial outcomes
- Clinical trial duration and cost

Param.	Preclinical	Phase 1	Phase 2	Phase 3
PoS (%)	60.0	83.6	65.8	80.9
Duration (months)	18.0	24.0	18.0	14.0
Cost ($ million)	26.0	14.0	28.0	150.0

Gouglas et al., 2018; Project ALPHA, 2021

	Chikun.	SARS	MERS	Marburg	RVF	Lassa	Nipah	CCHF	WNV	Zika
Chikun.	1.00	0.30	0.30	0.37	0.27	0.39	0.38	0.29	0.38	0.33
SARS	0.30	1.00	0.58	0.32	0.21	0.25	0.28	0.26	0.29	0.28
MERS	0.30	0.58	1.00	0.33	0.20	0.25	0.28	0.26	0.29	0.28
Marburg	0.37	0.32	0.33	1.00	0.27	0.37	0.46	0.37	0.36	0.35
RVF	0.27	0.21	0.20	0.27	1.00	0.48	0.29	0.52	0.27	0.26
Lassa	0.39	0.25	0.25	0.37	0.48	1.00	0.36	0.35	0.40	0.40
Nipah	0.38	0.28	0.28	0.46	0.29	0.36	1.00	0.32	0.39	0.39
CCHF	0.29	0.26	0.26	0.37	0.52	0.35	0.32	1.00	0.29	0.28
WNV	0.38	0.29	0.29	0.36	0.27	0.40	0.39	0.29	1.00	0.64
Zika	0.33	0.28	0.28	0.35	0.26	0.40	0.39	0.28	0.64	1.00

Correlation matrix of vaccine trial outcomes calibrated by biomedical similarity of pathogens

Sensitivity Analysis: mRNA Technology

- Increasing probability of success for mRNA technology increases both the number of approved vaccines and total investment
- Revenue of vaccine sales increases less significantly

Price Per Dose	E[R_a]	SD[R_a]	E[NPV] ($B)	E[Inv] ($B)
α_{tech}= 1.0	−6.7%	11.9%	−8.1	15.2
α_{tech} = 1.1	−6.2%	9.1%	−8.8	16.4
α_{tech} = 1.2 (baseline)	−6.0%	6.7%	−9.5	17.7
α_{tech} = 1.3	−5.8%	4.8%	−9.9	18.7

Estimating Clinical Trials Success Rates

Biostatistics (2019) **20**, 2, *pp.* 273–286
doi:10.1093/biostatistics/kxx069
Advance Access publication on January 31, 2018

Estimation of clinical trial success rates and related parameters

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SUMMARY

Previous estimates of drug development success rates rely on relatively small samples from databases curated by the pharmaceutical industry and are subject to potential selection biases. Using a sample of 406 038 entries of clinical trial data for over 21 143 compounds from January 1, 2000 to October 31, 2015, we estimate aggregate clinical trial success rates and durations. We also compute disaggregated estimates across several trial features including disease type, clinical phase, industry or academic sponsor, biomarker presence, lead indication status, and time. In several cases, our results differ significantly in detail from widely cited statistics. For example, oncology has a 3.4% success rate in our sample vs. 5.1% in prior studies. However, after declining to 1.7% in 2012, this rate has improved to 2.5% and 8.3% in 2014 and 2015, respectively. In addition, trials that use biomarkers in patient-selection have higher overall success probabilities than trials without biomarkers.

Estimating Probabilities of Success of Vaccine and Other Anti-Infective Therapeutic Development Programs

by Andrew W. Lo, Kien Wei Siah, and Chi Heem Wong

Published: May 14, 2020

HDSR
HARVARD DATA SCIENCE REVIEW

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Table 2. *The POS by therapeutic group, using data from January 1, 2000, to October 31, 2015. We computed this using the path-by-path method. SE denotes the standard error*

All indications (industry)

	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic group	Total paths	$POS_{1,2}$, % (SE, %)	Total paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	17 368	57.6 (0.4)	6533	32.7 (0.6)	6.7 (0.3)	1236	35.5 (1.4)	3.4 (0.2)
Metabolic/ Endocrinology	3589	76.2 (0.7)	2357	59.7 (1.0)	24.1 (0.9)	1101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2810	73.3 (0.8)	1858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4924	73.2 (0.6)	3037	51.9 (0.9)	19.5 (0.7)	1156	51.1 (1.5)	15.0 (0.6)
Autoimmune/ Inflammation	5086	69.8 (0.6)	2910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious disease	3963	70.1 (0.7)	2314	58.3 (1.0)	35.1 (1.0)	1078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (Infectious Disease)	1869	76.8 (1.0)	1235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41 040	66.4 (0.2)	21 180	58.3 (2.3)	35.1 (2.2)	7532	59.0 (0.6)	13.8 (0.2)
All without oncology	23 672	73.0 (0.3)	14 647	27.3 (0.4)	27.3 (0.4)	6296	63.6 (0.6)	20.9 (0.3)

Vaccine Success Rates

Harvard Data Science Review

Estimating Prob
Success of Vacc
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Therapeutic De
Programs

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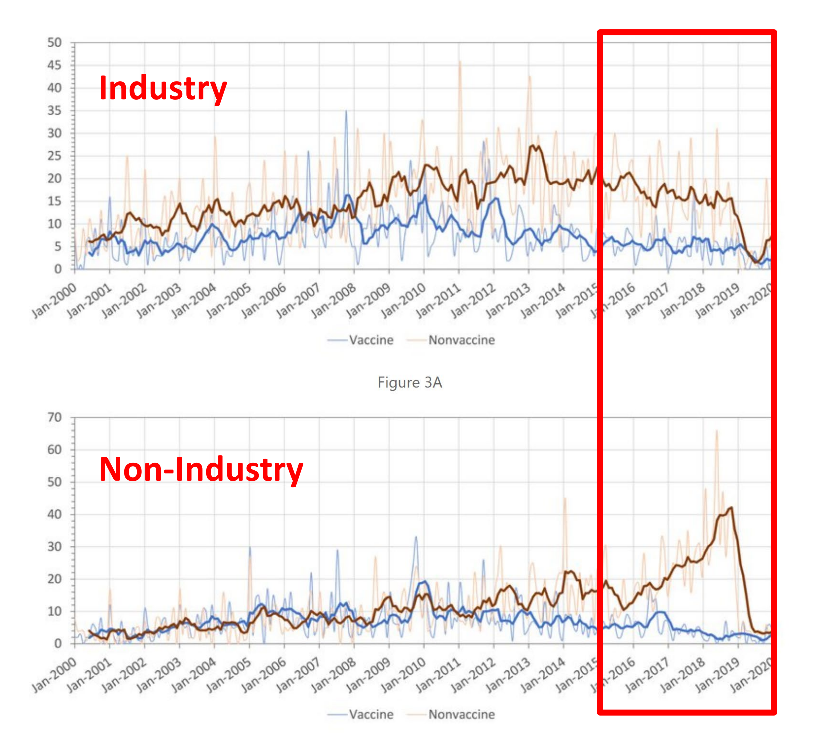

Figure 3A

Figure 3B