

Current Overview of COVID Vaccines as of 10th June 2021



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Student of DTM&H 2021

School of Tropical Medicine and Global Health, Nagasaki Univ.

My background – Who I am

No COI

Family physician for 18 years

- Outpatient and home care based

Special interests to **Vaccines** in the latter half of FP career

- As well as to **Travel medicine**; CTH by ISTM in 2008

Airport Quarantine Officer for 4 years

- Chubu Airport Quarantine Office

Planning xxx after finishing DTM&H...

My works and activities associated with COVID-19 and COVID vaccines

CareNet TV 配信予定 総合内科専門医試験 医学生 日案研修 FAQ CareNetTVとは DVD付アンケート ログイン

新着番組 ランキング 傑作選 スクール 講師別 診療科別

プロ仕様の PPE着脱も実演解説

病医院のための COVID-19対策Webセミナー

元診療所医師・現検疫官が教える「今現場でなすべきこと」

ライブストリーミング配信日：2020年3月5日

名古屋検疫所 中部空港検疫所支所 検査衛生課 医師 守屋章成氏

CareNet

- 個人医師個人チャンネルにアクセス(1日1回まで)
- 日タイマーリング スタンプを確認
- ケアネット会員限定! 会員特典
- 本日の臨床×クイズ
- クイズに答えて アップを獲得する
- 【告知用一部市】一般内科/麻酔外来【高年取2000...
- 告知用一般年取1000円〜

ワクチンと新型コロナウイルスと検疫【今、知っておきたいワクチンの話】総論 第5回

このコンテンツは、一般社団法人日本プライマリ・ケア 予防医療・健康増進委員会ワクチンチームと共同で、ならびにワクチンで予防できる疾患の知識を医療者に広を目的に制作されたコンテンツです。

日常診療に役立つ予防接種について、その制度の概要のワクチンについて、わかりやすく解説していただきま

筆者は家庭医として長年予防接種および遠航医学に従事疫官に転じて空港検疫所で勤務している。

第61回 日本臨床ウイルス学会 特別企画 COVID-19-19人の専門家からのアップデート

9. 臨床像 忍野 賢志	10. 重症例 川名 明彦
11. COVID-19の薬物治療 土井 淳平	12. 医療施設におけるCOVID-19の対応のポリシー(後編) 堀 賢
13. COVID-19と小児 森内 浩幸	14. COVID-19と妊婦 池田 智明
15. クラスター班の活動 押谷 仁	16. 流行予測 西浦 博
17. クルーズ船・ダイヤモンドプリンセス号船尾 山岸 拓也	18. 検疫所での対応 守屋 章成
19. 武漢からの帰国者対応 細川 直登	コーディネーター 学校閉鎖のインパクト 賢藤 啓彦

PCR検査を理解するために

Overview

Summary

- PCR法に代表される核酸増幅検査は、技術的には敏感な検査であるが、増幅機体では偽陽性が避けられない。
- 理論的には偽陽性はないとされるが、現実にはヒューマンエラーによる偽陽性が発生する。
- COVID-19に対してPCR検査を行う際には、偽陽性・偽陰性があることを考慮し、検査前確率の見積もりと検査後確率の適切な評価が不可欠である。
- 検査結果だけに振り回されることなく、確率的に検討する姿勢を大切にして

PCR検査の原理

PCRとは polymerase chain reaction (ポリマーゼ連鎖反応)の略である。生きたウイルスのDNAを複製し、増幅させることにより、検出可能なレベルまで増幅させる。その増幅したDNAをPCRによって検出する。

本稿を依頼いただいた2020年6月当時は、インターネットでもメディアでも「新型コロナウイルスのPCR検査の拡大論議」が喧しかった。日本の新型コロナウイルスのPCR検査数は海外国に比べて見劣りするの事実で、全くに緊急事態宣言後の4月後半に「国においては検査が数回でも検査が行えない事実も多かった」という点に同意する。しかし、検査拡大論のなかには、「全住民(全国民)に検査を『同一集団に対して毎週繰り返す検査を』希望者にはいつでも何度でも検査を」などの“過激”な主張も少なくなかった。そうした主張の背景の一に、感染・発症などの検査陽性が理解されにくいことがあげられると懸念される。いわゆる第2波がピークを過ぎた本稿執筆時の9月にはPCR議論はやや下火になったが、今こそ新型コロナウイルスのPCR検査を正しく理解し、検査に振り回されない“基礎体力”を身に付けたい。

キーワード：PCR、感度、特異度、検出感度、偽陽性、偽陰性

守屋章成 PRESENTS 特集 新型コロナワクチン今わかって いることまだわからないこと

1. 新型コロナワクチン接種開始にあたって

2020年1月10日に中国保健当局が新型コロナウイルス遺伝子の全塩基配列を公表した。その日から、世界中でワクチン開発レースが始まった。それからわずか11か月後の同年12月に、ファイザー社¹⁾(米国)、モデルナ社²⁾(米国)、アストラゼネカ社³⁾(英国)が相次いで英文査読誌に治験第3相の論文を掲載した。いずれも高くべき高き効果と安全性が示されており、世界はワクチンによる新型コロナ収束に光明を見出すこととなった。

しかし、「ウイルス遺伝子を人体に接種する」という新規の技術による開発であり、医師医療職の関与で安全性に懸念した不安を上げる声が多かった。

本稿では2021年2月17日現在で報告されている最新の情報に基づいて、3社の新型コロナワクチンの効果、安全性、接種時の検討事項、未検証項目および金銭的注点について整理した。上梓された日が白いワクチンであり、今後も複雑な情報更新が予想され



Today's talk: "non-systematic review" of medical literatures of COVID vaccines

Around **100 original articles/correspondences** relevant to COVID vaccines reviewed

- **1-3 new medical articles** being added **every week** since December 2020


NOTICE: All of today's discussions are **subject to change** according to the progresses of medical researches and expansion of COVID vaccine uptake all over the world

- **Keep your eyes on every new article!**

- 1. Classification** of COVID vaccines
- 2. Vaccine efficacy/effectiveness** of COVID vaccines
- 3. Reactogenicity** and **anaphylaxis** due to COVID vaccines
- 4. Unexpected severe adverse events/** how to interpret reported adverse events
- 5. What to consider and how to decide to vaccinate **specific subpopulations****
- 6. Will COVID vaccines make us free** from facemask and life restrictions?

1. Classification of COVID vaccines



One of world's oldest COVAC bottle on Mt. Unzen,  settled far before the pandemic (taken on 6th June 2021)

1. COVID vaccine development – **spike (S) protein** is the target antigen

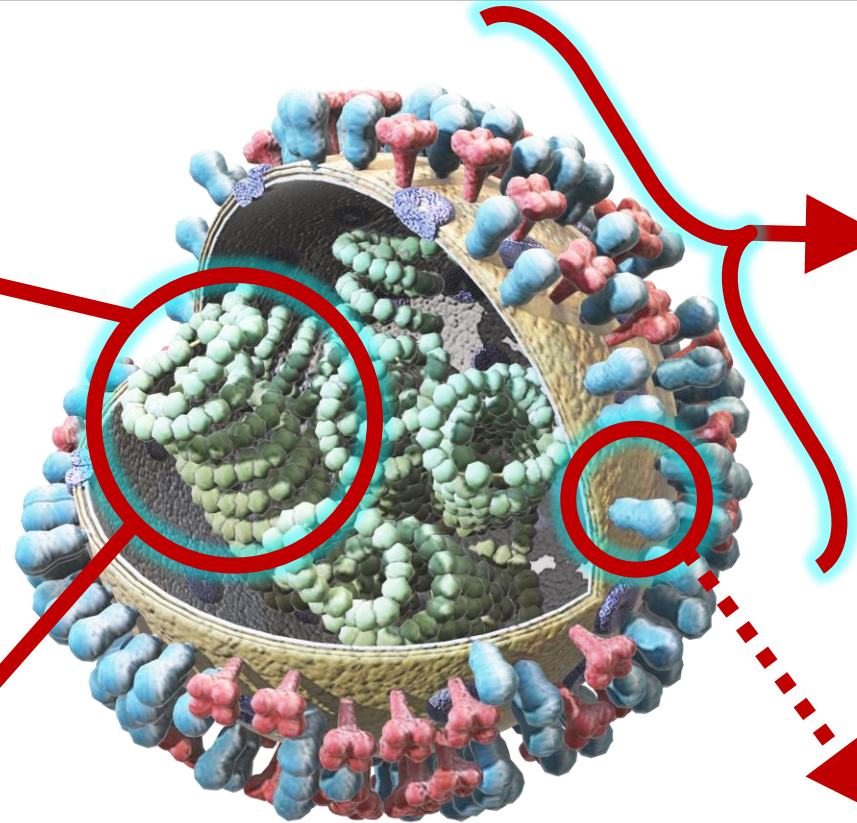
mRNA vaccine

- **Fragment of RNA** coding spike protein
- RNA wrapped by **PolyEthylene Glycol**
- **Human muscle cells produce S protein**



Viral vector vaccine

- S protein coding sequence **embedded in a harmless virus**
- **Human muscle cells produce S protein**



Inactivated vaccine

- **The virus itself** cultured, inactivated and destroyed with chemicals
- **Contains S protein**



Protein-based vaccine

- Produce S protein by **genetically recombinant plant virus**



1. Classification of currently approved COVID vaccines

Class	Pharma	Code name	Dosing	Countries approved/EUA	
mRNA	Pfizer-BioNTech /US	BNT162b2	0, 21d	US, EUs, UK, JP, Israel, ... > 50	Total uptake all over the world: 2.02 billion doses as of 3 June 2021
	Moderna /US	mRNA-1273	0, 28d	US, EUs, JP, ... > 20	
Viral vector	Oxford-AstraZeneca	ChAdOx1	0, 12w?	UK, EUs, JP, PH, ... > 80	
	Johnson-Johnson /US	Ad26.COV2.S	Single	US, UK, EUs, PH, ... > 20	
	Gamaleya /Russia	Sputnik V	0, 21d	Russia, DRC, PH, ... > 60	
	CanSino /China	Ad5-nCoV	Single	China, Hungary, ... 6	
Inactivated	Sinopharm /China	BBIBP-CorV	0, 21d	China, UAE, Hungary, ... > 30	
	Sinopharm-Wuhan	WIV04/HB02	0, 21d	China, UAE. 2	
	Sinovac / China	CoronaVac	0, 14d	China, TH, Brasil, ... > 20	
	Bharat Biotech /India	BBV152A,B,C	0, 28d	India, PH, Nepal, ... 12	

*There are some other vaccines approved/EUA in fewer countries including Protein-based vaccine

2. COVID Vaccine efficacy/effectiveness



2. Vaccine efficacy in **phase 3 trials** against **symptomatic COVID**

Class	Pharma	Code name	VE	DOI of articles
mRNA	Pfizer-BioNTech /US	BNT162b2	95.0%	10.1056/NEJMoa2034577
	Moderna /US	mRNA-1273	94.1%	10.1056/NEJMoa2035389
Viral vector	Oxford-AstraZeneca	ChAdOx1	70.4%	10.1016/S0140-6736(20)32661-1
	Johnson-Johnson /US	Ad26.COV2.S	66.9%	10.1056/NEJMoa2101544
	Gamaleya /Russia	Sputnik V	91.6%†	10.1016/s0140-6736(21)00234-8
	CanSino /China	Ad5-nCoV	65.28%*	(*Governmental release only)
Inactivated	Sinopharm /China	BBIBP-CorV	78.1%*	(*Governmental release only)
	Sinopharm-Wuhan	WIV04/HB02	72.8%	10.1001/jama.2021.8565
	Sinovac / China	CoronaVac	50.65%†	(†Pharma press release only)
	Bharat Biotech /India	BBV152A,B,C	78%†	(†Pharma press release only)

† just before the 2nd shot

2. Vaccine efficacy in **phase 3 trials** against **symptomatic COVID**

mRNA vaccines **fairly** reduce **symptomatic COVID**

- Approximately **95%**

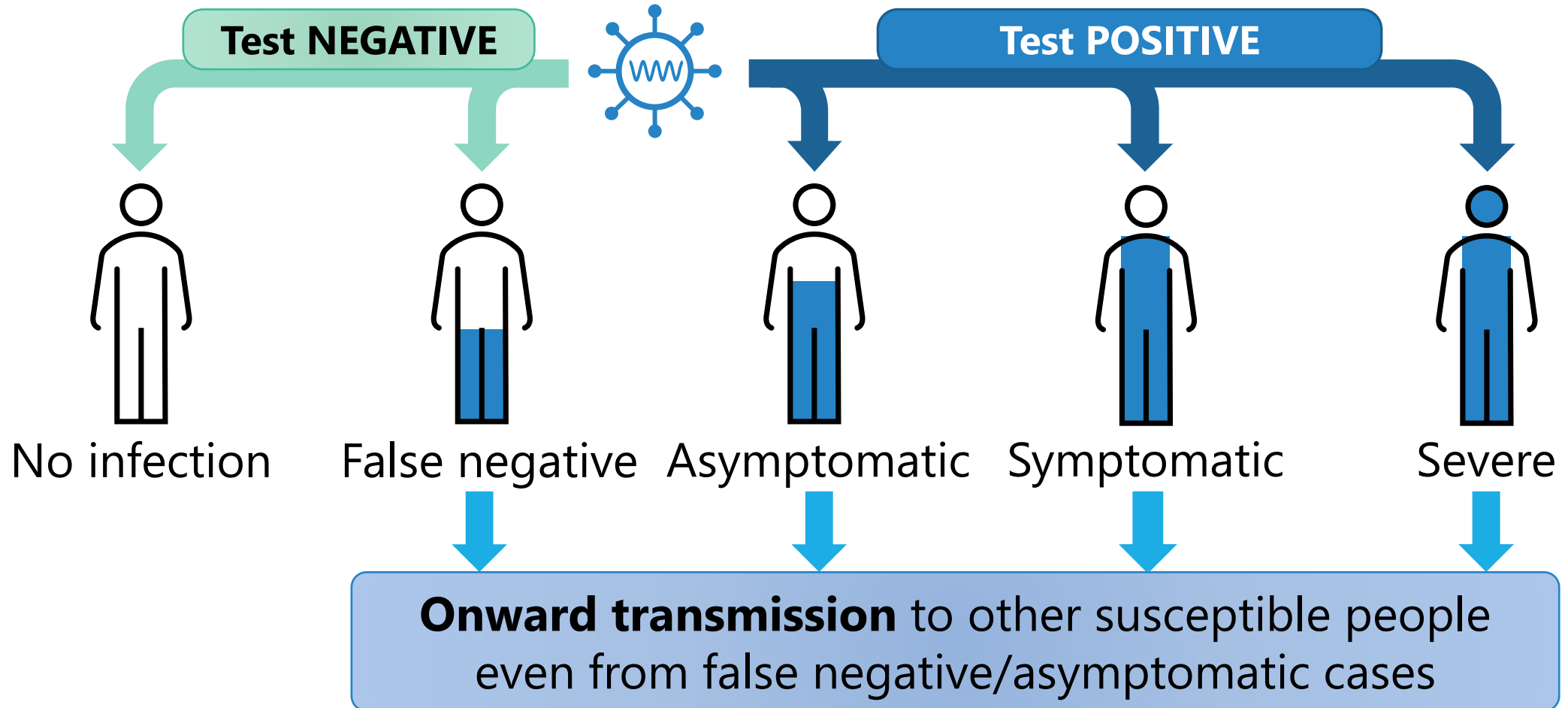
Viral vector vaccines **moderately** reduce **symptomatic COVID**

- Ranging **65 to 90%**

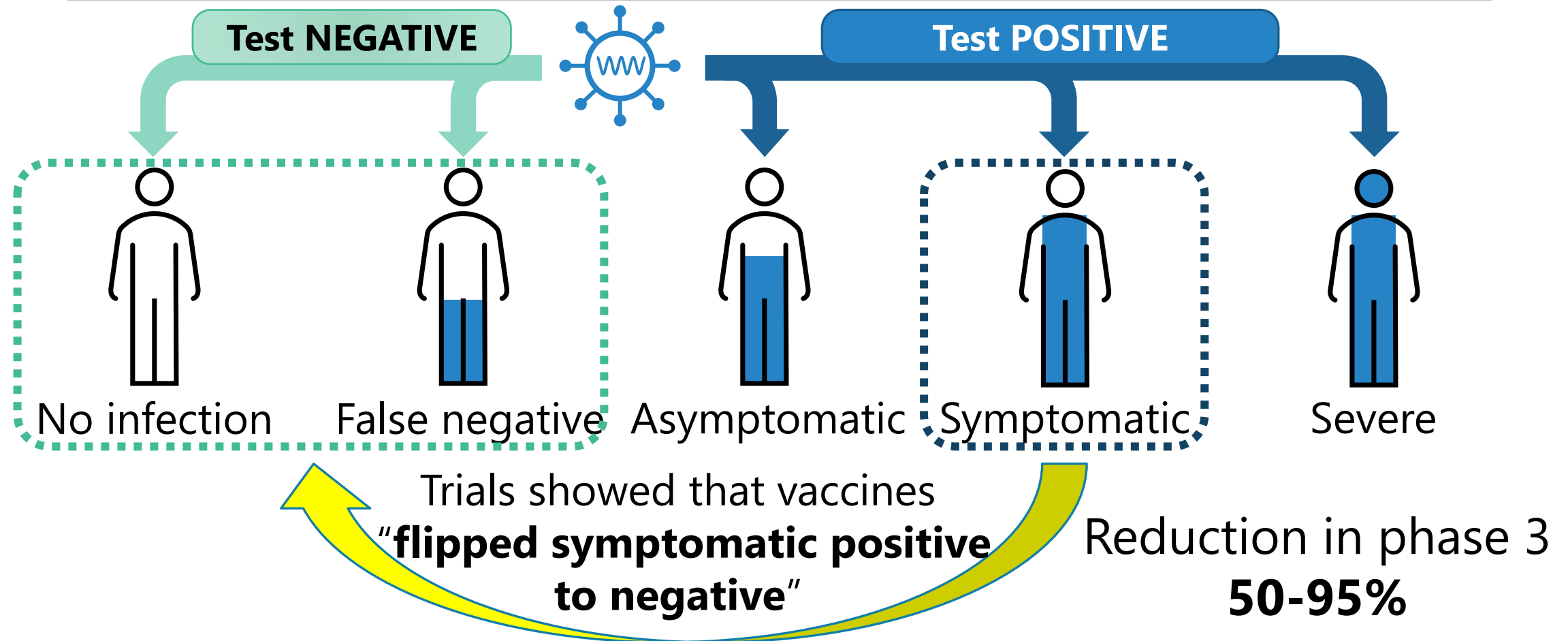
Inactivated vaccines **mildly** reduce **symptomatic COVID**

- Ranging **50 to 80%**

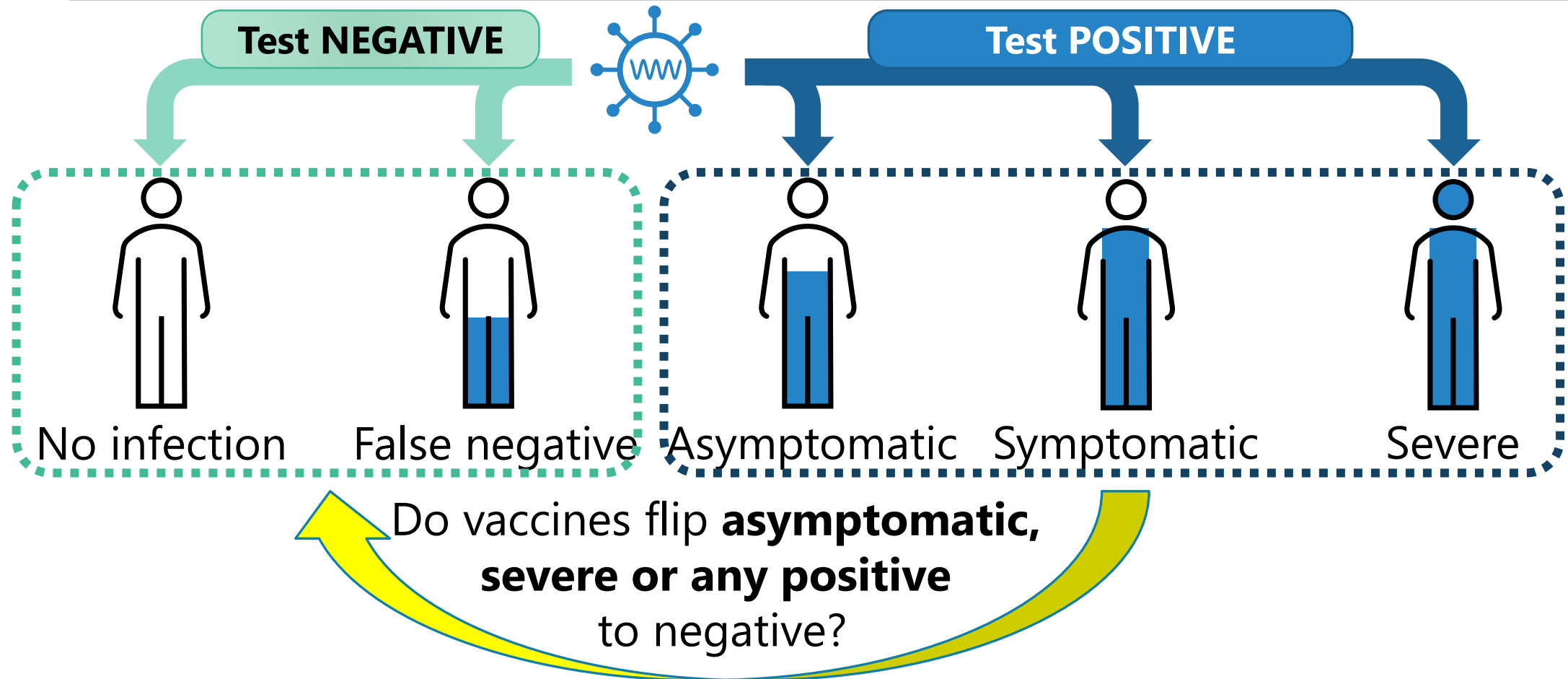
2. What happens on individuals after exposure to SARS-CoV-2



2. Vaccines reduce **symptomatic** COVID - means "flipping positive to negative"



2. Do vaccines reduce other form of COVID positivity **in real world**?



Again

2. Vaccine efficacy in **phase 3 trials** against **symptomatic COVID**

Class	Pharma	Code name	VE	DOI of articles
mRNA	Pfizer-BioNTech /US	BNT162b2	95.0%	10.1056/NEJMoa2034577
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Viral vector	Oxford-AstraZeneca	ChAdOx1	70.4%	10.1016/S0140-6736(20)32661-1
	Johnson-Johnson /US	Ad26.COV2.S	66.9%	10.1056/NEJMoa2101544
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	CanSino /China	Ad5-nCoV	65.28%*	(*Governmental release only)
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	Bharat Biotech /India	BBV152A,B,C	78%†	(†Pharma press release only)

† just before the 2nd shot

2. Vaccine effectiveness in real world being established only in 3 so far

Class	Pharma	Code name	VE	DOI of articles
mRNA	Pfizer-BioNTech /US	BNT162b2	95.0%	10.1056/NEJMoa2034577
	Moderna /US	mRNA-1273	94.1%	10.1056/NEJMoa2035389
Viral vector	Oxford-AstraZeneca	ChAdOx1	70.4%	10.1016/S0140-6736(20)32661-1
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	CanSino /China	Ad5-nCoV	65.28%*	(*Governmental release only)
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† just before the 2nd shot

2. Vaccine effectiveness in real world – Pfizer & Moderna mRNA vaccines

DOI	Published	Country	Research design	Vaccines	Samples	Symptomatic	Hospitalized	Severe	Asymptomatic	Any
10.1056/NEJMoa2101765	Feb.	Israel	Historical cohort	Pfizer	1.2 million citizens	92	87	92	90	—
10.1093/cid/ciab229	Mar.	US	Historical cohort	Pfizer & Moderna	39,156 patients screened before procedures	—	—	—	80	—
10.15585/mmwr.mm7013e3	Mar.	US	Prospective cohort	Pfizer & Moderna	3,950 healthcare workers	—	—	—	—	90
10.1016/S0140-6736(21)00790-X	Apr.	UK	Prospective cohort	Pfizer	23,324 HCWs				—	86
10.1016/S0140-6736(21)00947-8	May	Israel	Historical cohort	Pfizer	6.54 million citizens	97.0	97.2	97.5	91.5	95.3

mRNA vaccines reduce (flip positive to negative) to the degree of **approximately 90%**

2. Vaccine effectiveness in real world – Oxford viral vector vaccine

2 doses	DOI	Published	Country	Research design	Doses	Samples	Symptomatic	Hospitalized	Severe	Asymptomatic	Any
	10.1016/S0140-6736(21)00432-3	Mar.	UK	After phase 3 trial	Two	Trial participants 17,178	63.1	–	–	NS	49.5

Single dose	DOI	Published	Country	Research design	Samples	Outcome	7-13 days	14-20 days	21-27 days	28-34 days	35-41 days	42+ days
	10.2139/ssrn.3789264	Feb.	UK	Prospective cohort	5.4 million citizens	Hospitalized	70	74	84	94	NA 51 vs 0	NA 1 vs 0
	DOI	Published	Country	Research design	Samples	Outcome	22-30 days	31-60 days	61-90 days	22-90 days total	91-120 days	
	10.1016/S0140-6736(21)00432-3	Mar.	UK	After phase 3 trial	17,178 trial participants	Symptomatic	76.7	72.8	78.3	76.0	NS	
					Asymptomatic	NS	NS	NS	NS	NS		
					Any	62.3	56.3	79.4	63.9	NS		

2 doses of Oxford vaccines reduce (flips positive to negative) to the degree of **50 to 60%**
Single dose of Oxford vaccine keeps its effectiveness **3 months at the longest**

2. Vaccine effectiveness in real world – against variants

WHO label	Pango lineage	So called...	DOI	Study design	Pfizer	Moderna	Oxford
Alpha	B.1.1.7	UK stain	10.1056/NEJMc2104974	Test negative case control	Any: 89.5 Severe: 100	–	–
			10.1101/2021.05.22.21257658	Test negative case control	Any: 93.4	–	Any: 66.1
Beta	B.1.351	South Africa strain	10.1056/NEJMoa2102214	RCT	–	–	Not effective
			10.1056/NEJMc2104974	Test negative case control	Any: 75.0 Severe: 100	–	–
Gamma	P.1	Brazil stain	(No true endpoint study so far)	–	–	–	–
Delta	B.1.617.2	India strain	10.1101/2021.05.22.21257658	Test negative case control	Any: 87.9	–	Any: 59.8

Against variants, Pfizer is fairly effective, Oxford moderately, Moderna unknown

2. mRNA and Oxford vaccines reduce any COVID positivity in real world

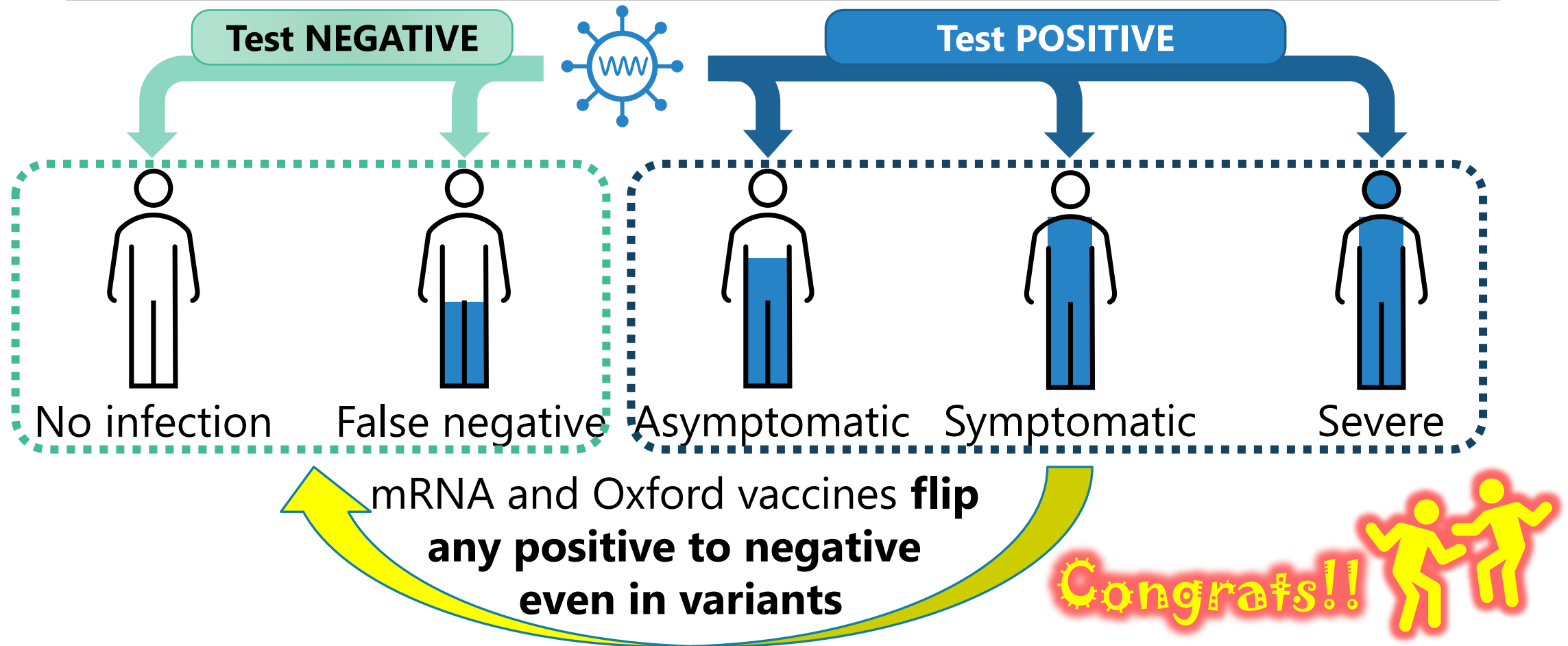
mRNA vaccines reduce any COVID

- Original strain \approx 90%
- Alpha, Beta, Delta variants \approx 75 to 90%

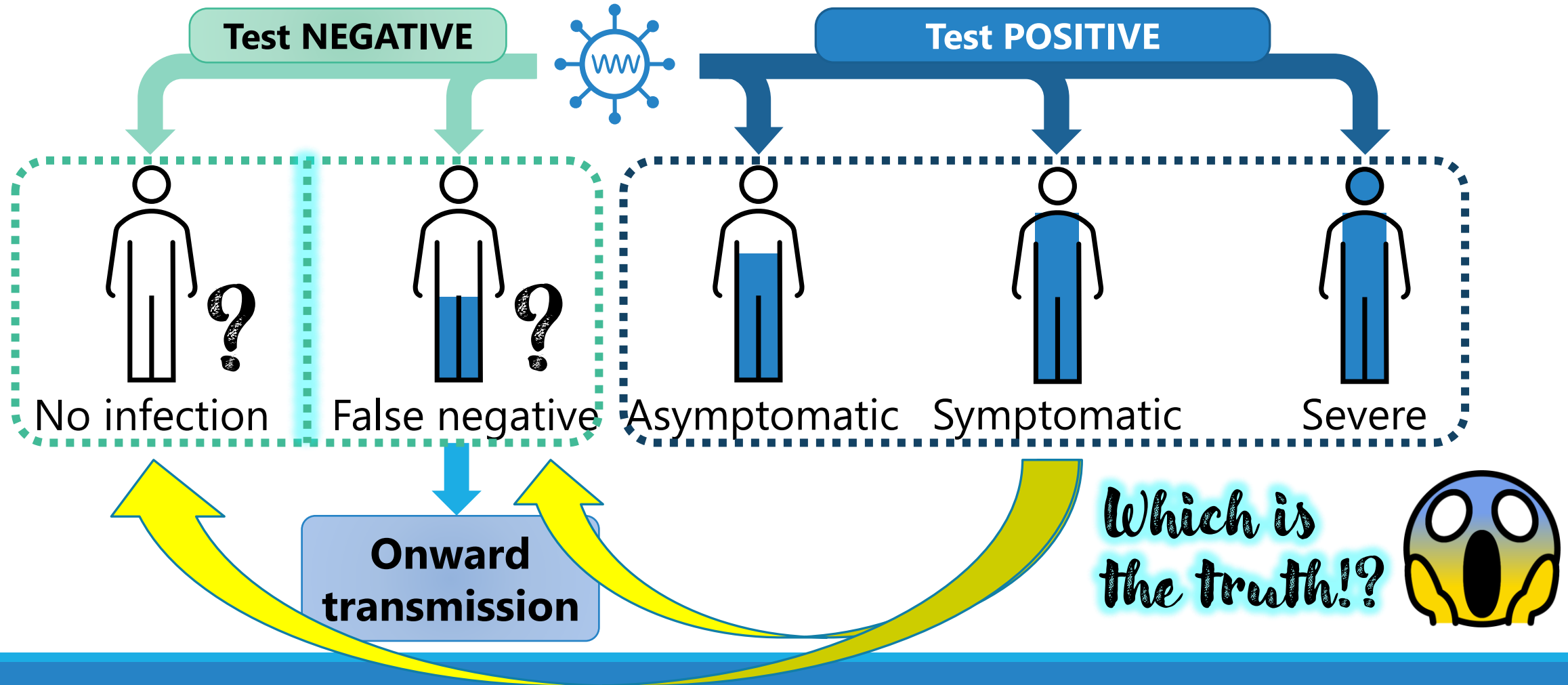
Oxford vaccine reduces any COVID

- Original stain \approx 50 to 60%
- Single dose \approx 70% up to 3 months
- Alpha, Delta variants \approx 60%

2. mRNA and Oxford vaccines reduce any COVID positivity in real world



2. But ... How about **False negativity**? Do the vaccinated **still transmit COVID**?



2. Proof of “truly no COVID” is *probatio diabolica* (devil’s proof)

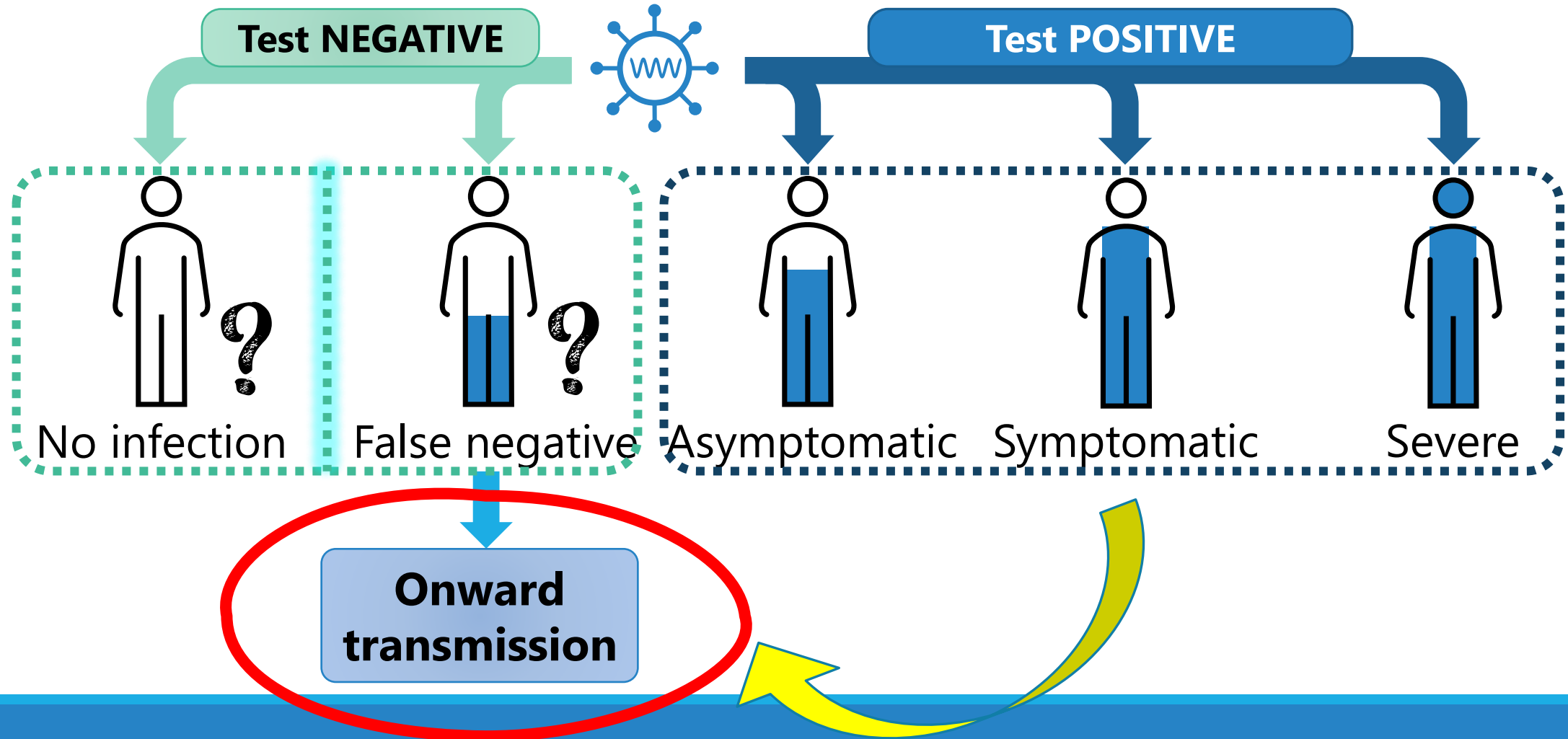
Any COVID tests are quite **less sensitive**

- Negative result cannot exclude infection

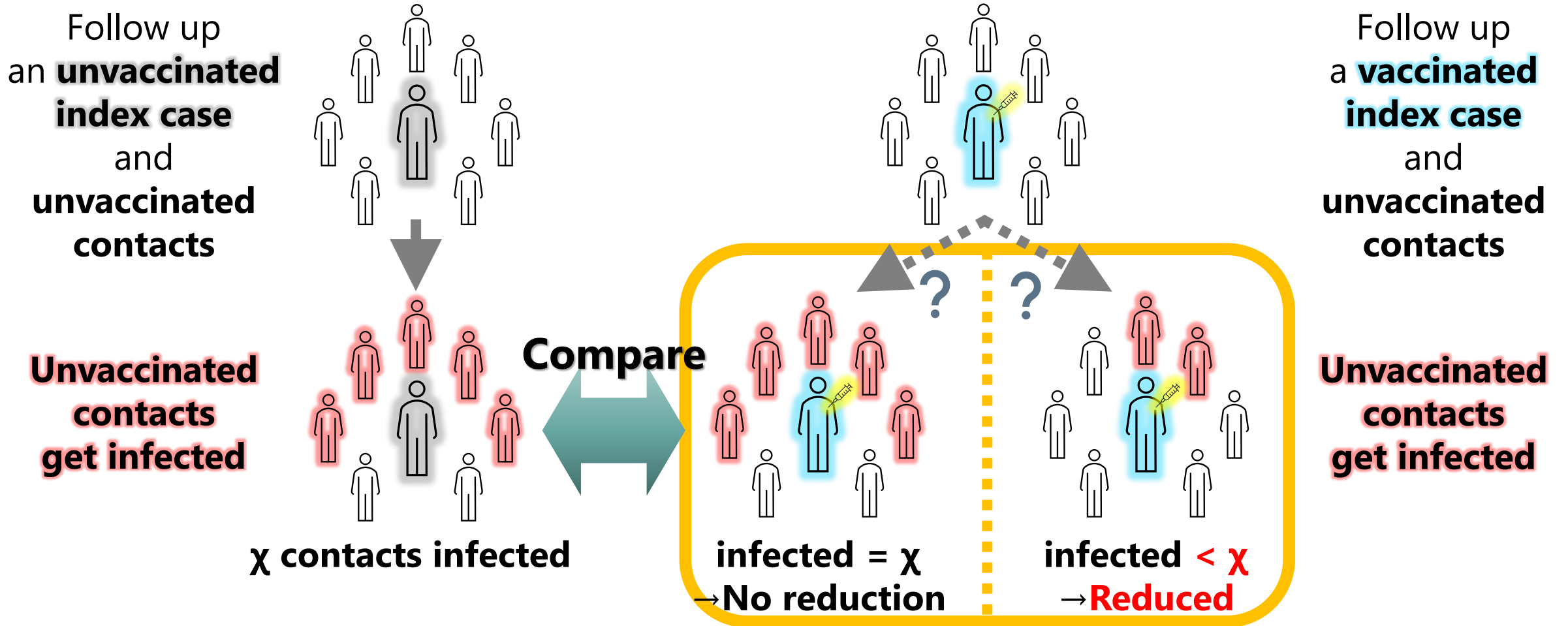
Alternative is proof of **reduction of onward transmission**

- If onward transmission is also reduced, it indirectly proves true negative
 - ... at least substantially low viral load enough to stop transmission

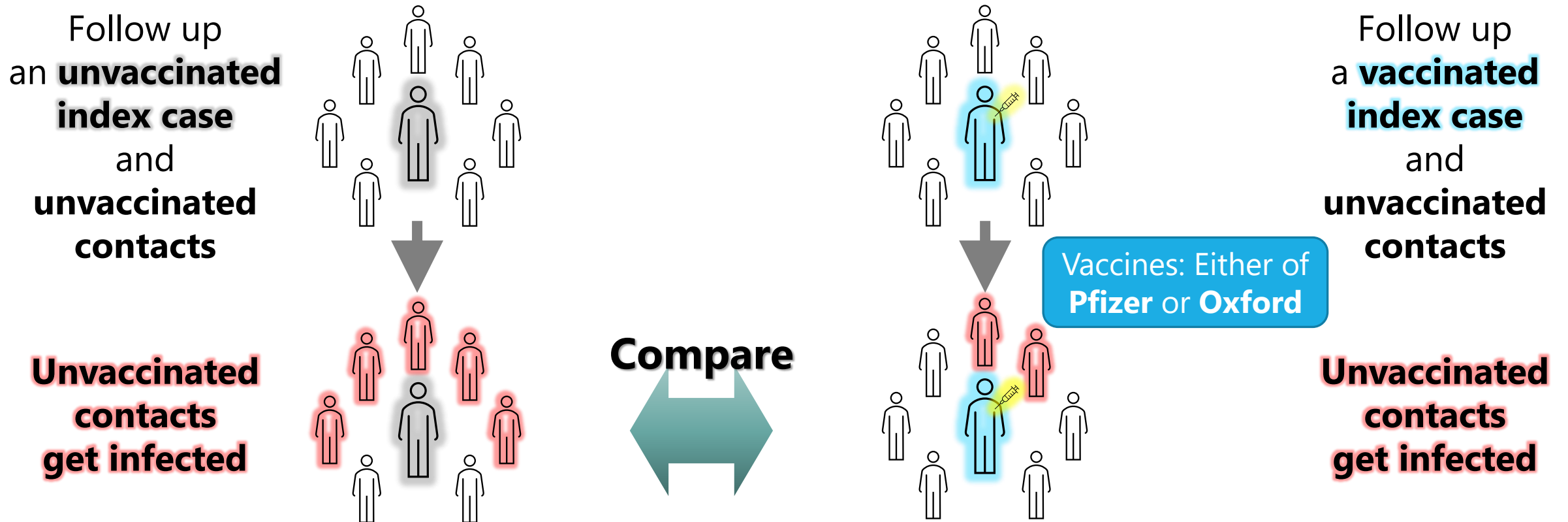
2. Let's look into **onward transmission** from **vaccinated people**



2. How to investigate reduction of onward transmission

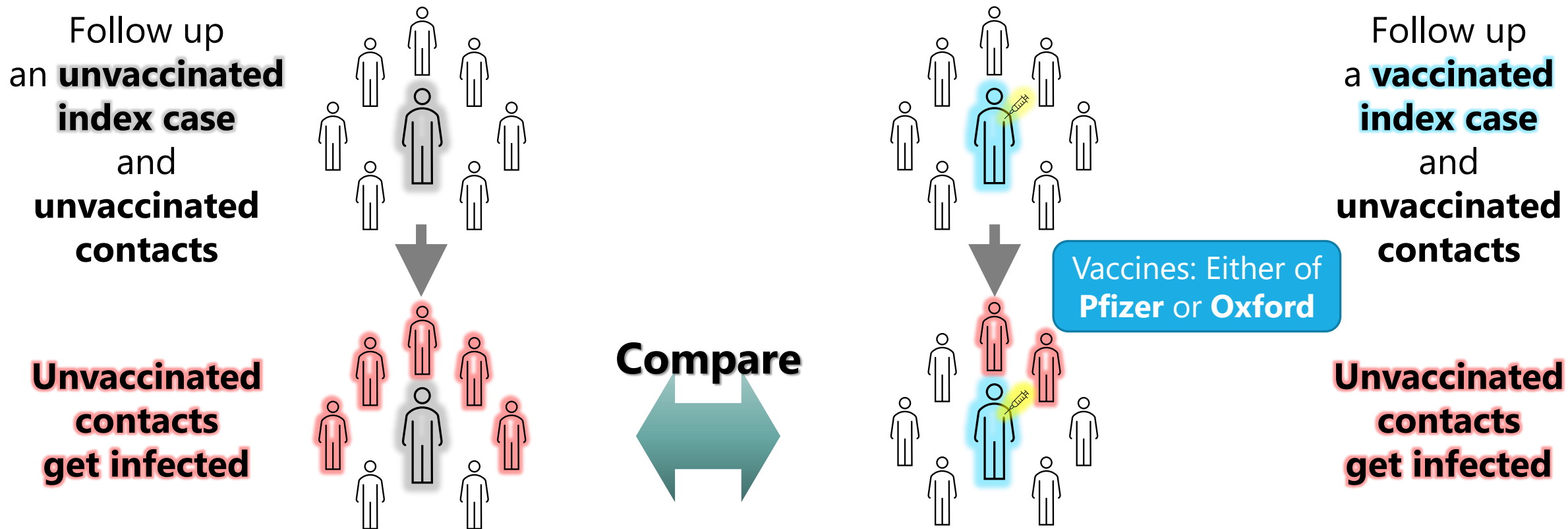


2. Study from Scotland, UK - Vaccinated HCWs and unvaccinated household



Hazard ratio of any **COVID** in unvaccinated contacts of **vaccinated** index cases compared to unvaccinated contacts of **unvaccinated** index cases was **0.46-0.50**

2. Study from England, UK - Vaccinated citizens and unvaccinated household



Odds ratio of any **COVID** in unvaccinated contacts of **vaccinated** index cases compared to unvaccinated contacts of **unvaccinated** index cases was **0.43-0.67**

2. Pfizer and Oxford vaccines **reduce onward transmission**

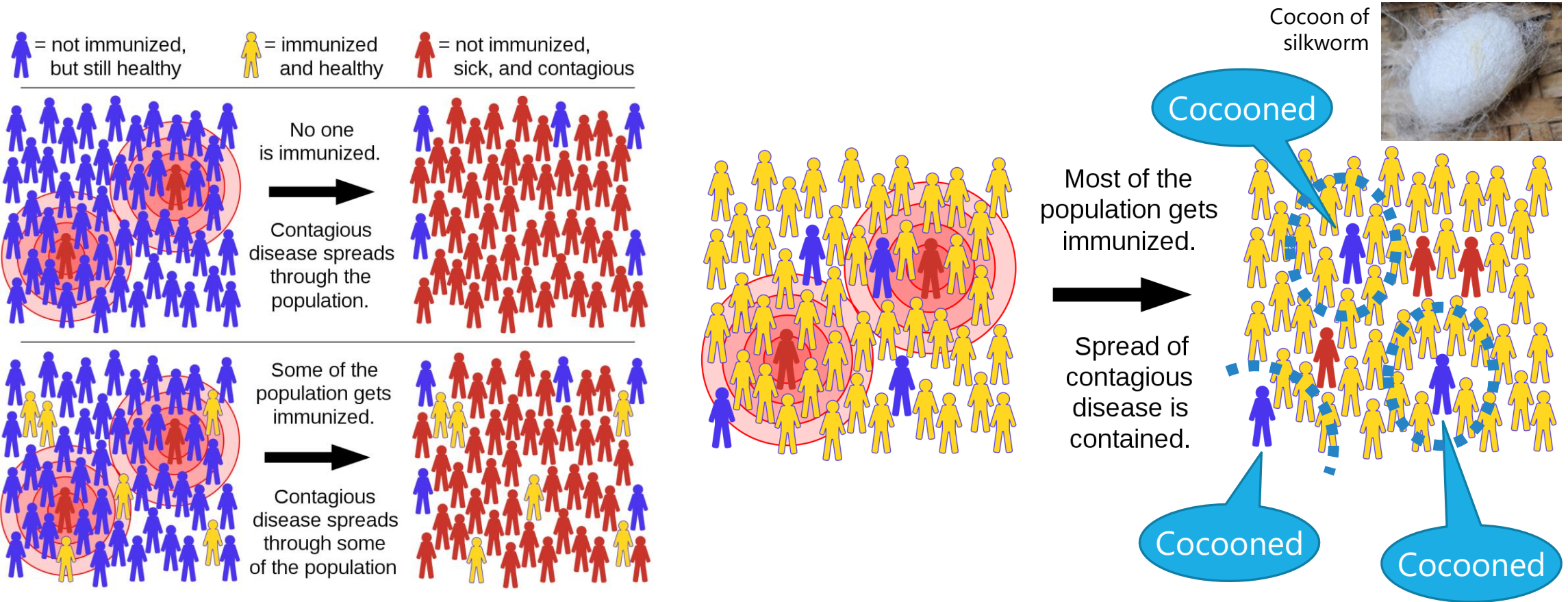
Pfizer and Oxford vaccines **reduce onward transmission** \approx 50%

- Hereat, please ignore the precise conversions of OR/HR to RR ...
- Reduction of onward transmission leads to **cocooning effect**

It suggests that the vaccines **make vaccinees truly free from infection** to a certain extent

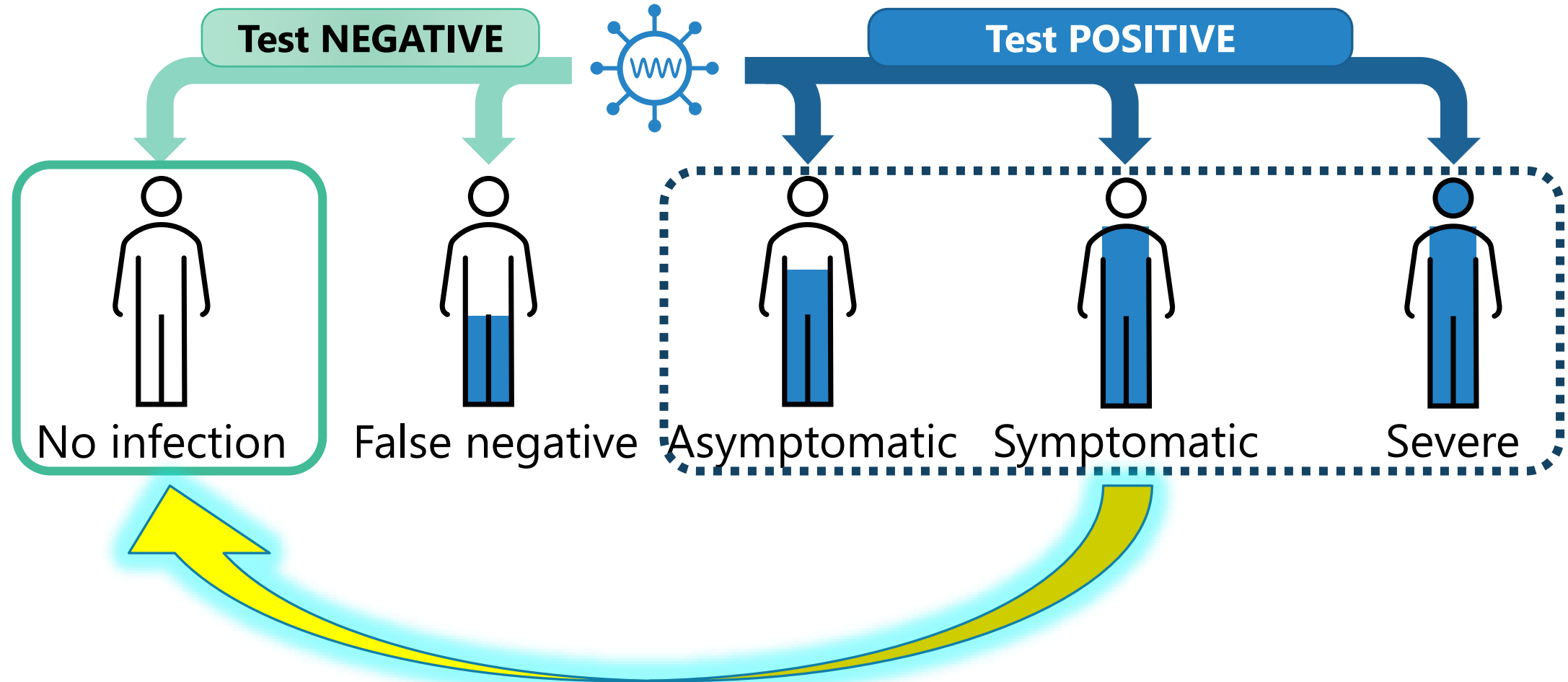
- "A certain extent" should be at least \approx 50%
 - Behavior of unvaccinated contact could be heterogenous and cannot adjust
- "A certain extent" might be around 90%, same as reduction of positivity

2. Pfizer and Oxford vaccines showed cocooning effect – herd immunity



(CC BY-SA 4.0; Adapted from Mediawiki)

2. mRNA and viral vector vaccines truly prevent infection! Congrats!!



3. Reactogenicity and Anaphylaxis



3. Reactogenicity is a subset of **natural reactions** to vaccination

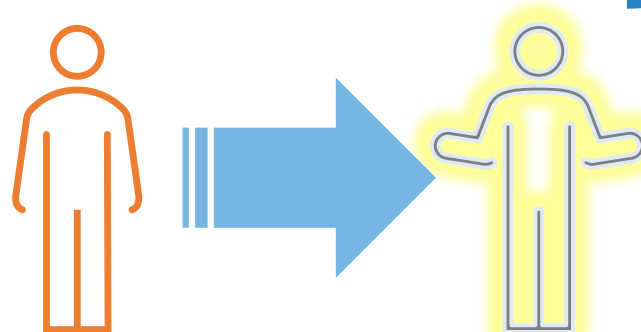
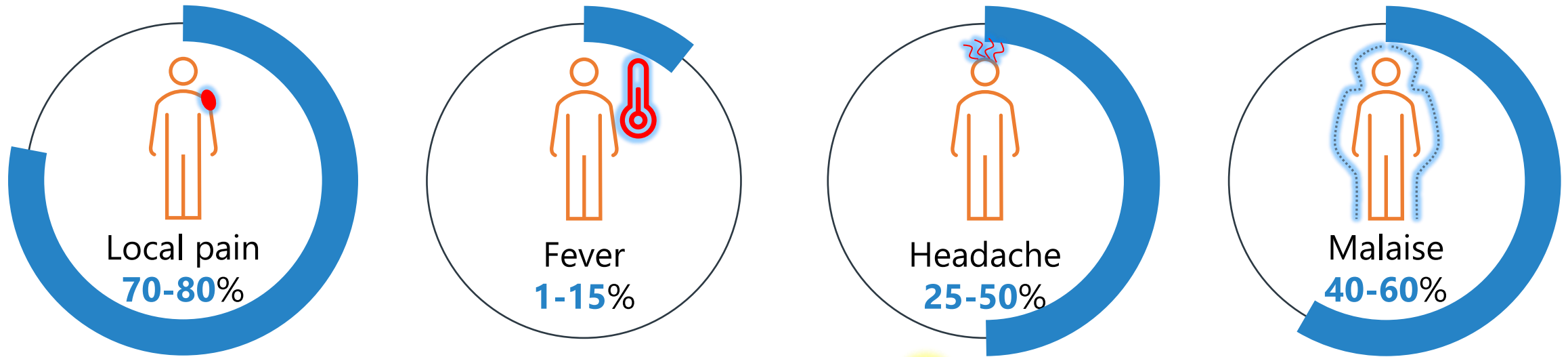
“Reactogenicity is a subset of reactions that occur soon after vaccination, physical manifestation of the **inflammatory response to vaccination**”

- DOI: 10.1038/s41541-019-0132-6

Local symptoms and systemic symptoms

- Pain, redness, swelling, induration, regional lymphadenopathy, etc.
- Fever, myalgia, arthralgia, headache, rash, etc.
- Natural and anticipated; even if no reaction, vaccine is definitely working! No worry!

3. Reactogenicity of COVID vaccines



- Spontaneously relieved within a few days
- 2nd shot more likely

3. Delayed local hypersensitivity skin reactions by Moderna vaccine

Almost specific to Moderna vaccine

Erythematous, relatively demarcated, pinky to red, large macule

Appear median **7-8 days after** each dose

- Range 2-14 days
- **After acute reactogenicity**

Spontaneously resolve in median **3-6 days**

- Range 1-21 days

Pathology: Delayed or T-cell mediated hypersensitivity reaction

NO CONTRAINDICATION for the 2nd dose

- More likely in 1st dose; can also occur in 2nd



“Moderna arm”

DOI:10.1056/NEJMc2102131
10.1016/j.jaad.2021.03.092
10.1001/jamadermatol.2021.1214

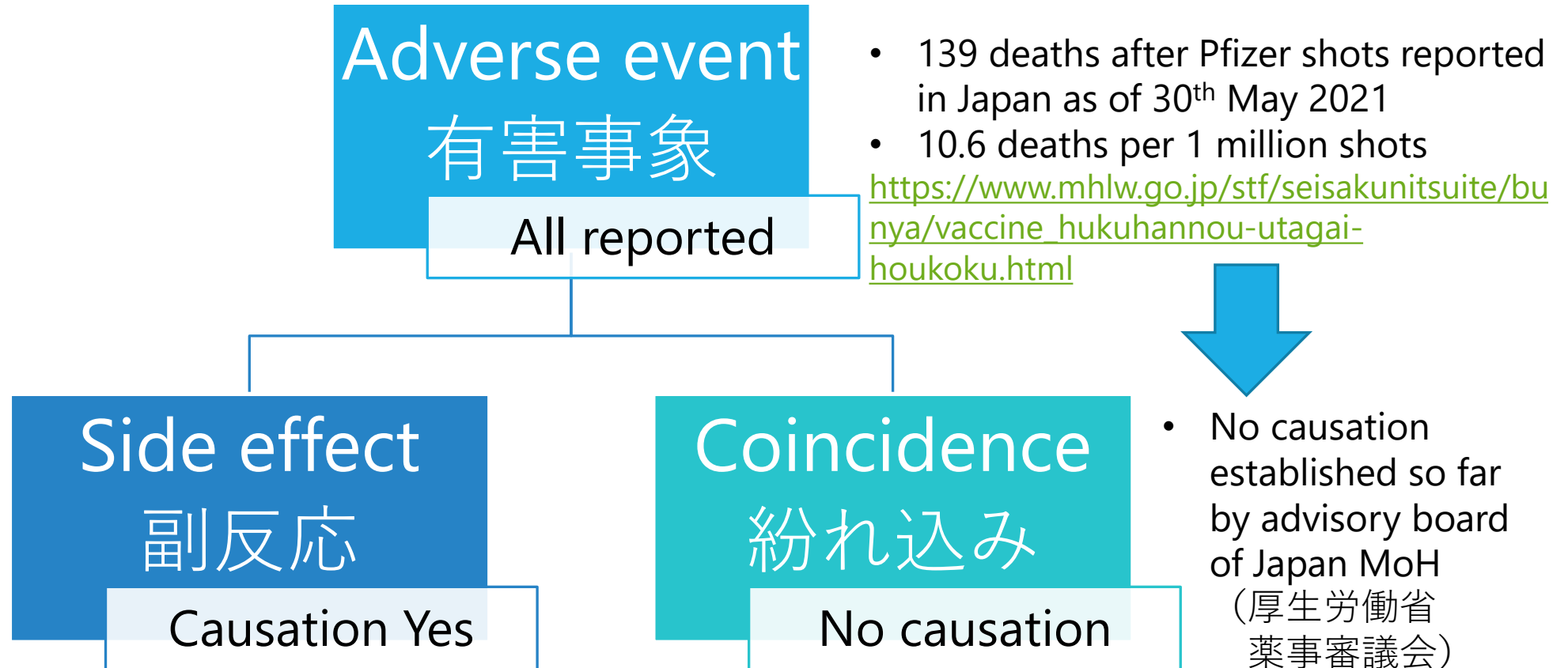
3. Anaphylaxis due to COVID vaccines

DOI	Vaccines	Incidence	Potential allergen
10.1001/jama.2021.1967	Pfizer	4.7 in 1 million vaccinations	Polyethylene glycol (PEG)
	Moderna	2.5 in 1 million vaccinations	Polyethylene glycol (PEG)
(not well published)	Oxford	(unknown well)	Polysorbate 80
(not well published)	Other COVID vaccines	(unknown well)	—
10.1016/j.jaci.2015.07.048	Inactivated influenza	1.3 in 1 million vaccinations	Egg proteins

- **Younger females** are much more prone to anaphylaxis due to mRNA vaccines than others
 - **PEG** frequently contained **in cosmetics** may be the reason, but **not yet established**
- Anaphylaxis was more frequent in earlier HCWs period of vaccination campaign – younger females?

4. Unexpected severe adverse events/ how to interpret them

4. Clearly distinguish three factors



4. Vaccine-induced Thrombotic Thrombocytopenia (**VITT**) – viral vector

DOI	Vaccine	Manifestations	Cases (deaths)	Demography	Timing
10.1056/NEJ Moa2104840	Oxford	Almost all: • Cerebral venous sinus thrombosis • Subsequent thrombocytopenia • Platelet 10,000 – 127,000 • Antibody to platelet factor 4 – heparin complex positive	11 (5)	22-49 y/o 9 of 11 female	5-16 days after the 1 st
10.1056/NEJ Moa2104882	Oxford		5 (2)	32-54 y/o 4 of 5 female	7-10 days after the 1 st
10.1056/NEJ Moa2105385	Oxford		23 (7)	21-77 y/o 14 of 23 female	6-24 days after the 1 st
10.1001/jama.2021.7517	Johnson Johnson		12 (3)	18 < <60 (unrevealed) All female	6-15 days after single

- Only associated with **viral vector vaccines**; no relevant report with mRNA vaccines
- Etiology **not yet established** including production of **PF4-heparin complex antibody**
- Incidence \approx **1-4 : 100,000 vaccinations** \Leftrightarrow CVST in general population **0.22-1.57 : 100,000**

4. Do mRNA vaccines have unexpected severe adverse events?

Immune thrombocytopenic purpura and **Bell's palsy** suggested, but **seems unassociated so far**

- **ITP** - DOI: 10.1002/ajh.26132; **Bell's palsy** - DOI: 10.1001/jamainternmed.2021.2219

mRNA vaccines have been shot at least **0.5 billion** worldwide;
Any extremely rare undiscovered AE would arise hereafter?

- Probability that "AE of 1 in 10 million **never occurs** among 0.5 billion shots"
$$= \left(1 - \frac{1}{10 \text{ million}}\right)^{0.5 \text{ billion}} = 1.93 \times 10^{-22} \dots \text{extraordinarily improbable}$$
- mRNA vaccines **would have no unexpected adverse events** so far and hereafter
- If any, unexpected adverse events **in specific subpopulations** would be uncovered

4. Are mRNA vaccines associated with myocarditis in adolescent?

I've just got the information a couple of hours before this presentation

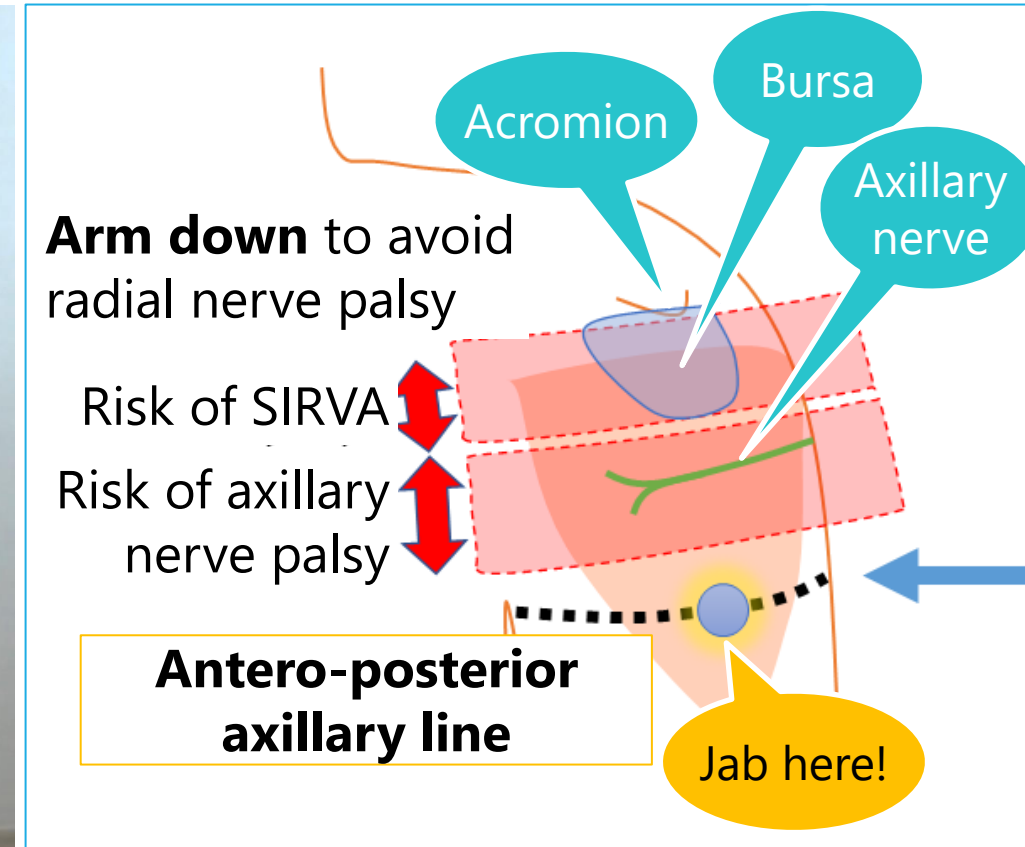
- Couldn't have enough time to investigate details. Sorry...

US-CDC announcement on 27th May 2021

<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html>

- Since April 2021, reports of myocarditis and pericarditis after mRNA vaccines those older than 16 y/o are increasing
- Currently CDC is gathering further information, but has not determined an association with mRNA vaccines and the conditions
- CDC does not think the US should suspend mRNA vaccines to adolescents or young adults

4. Avoid SIRVA* and radial/axillary nerve palsy at deltoid injection!



The video created and authorized by
Japan Primary Care Association

<https://www.youtube.com/watch?v=tA96CA6fJv8>

*SIRVA = Shoulder Injury Related to Vaccine Administration

4. References for our proposal of new deltoid injection site

DOI	DOI
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Great thanks to **Dr. Nakanishi** in Nara Medical University, an orthopedist who has advocated it and supervised us

5. Considerations for **specific subpopulations**

5. Considerations for specific subpopulations

Safety and/or effectiveness being established

DOI: 10.1001/jama.2021.7563
DOI: 10.1056/NEJMoa2104983

- Pregnant/breastfeeding women – no increase of AE observed
- Children over 12 years old – safe and effective US and Japan has already approved
- The oldest old (>85 years old) - safe Many evidences DOI: 10.1016/j.eclinm.2021.100914
- Previously COVID infection – recommended, reactogenicity may decrease in 2nd

Safety and/or effectiveness not enough

- Immunocompromised patients – may less effective DOI: 10.1053/j.ajkd.2021.05.004
- Cancer patients under chemo/radiotherapy – may cause specific reaction DOI: 10.1038/s41591-021-01387-6

5. Dedicated communication needed in vaccination for subpopulations

For pregnant and breastfeeding women

- “Do not easily link any pregnancy- or breastfeeding-related adverse events after your shots”
- “Have you enough communicated with each of stakeholders including your partner (husband), your parents and his parents?”

For immunocompromised or cancer patients

- Balancing matters between potential high COVID mortality, potential low vaccine effectiveness, potential worsening of the disease and potential unknown adverse effect
- Encourage to communicate and discuss with doctors in charge of the diseases

6. Will COVID vaccines
make us free?

6. Let's discuss whether vaccination will make us free or not

Medical point of view?

- How safe are vaccinated people?

Social point of view?

- Is "first come, first freed" ethical?

To accelerate vaccine uptake?

- Is incentivizing less interested people effective?