



IMMUNISATION  
COALITION

# Chronic complications of influenza and COVID-19

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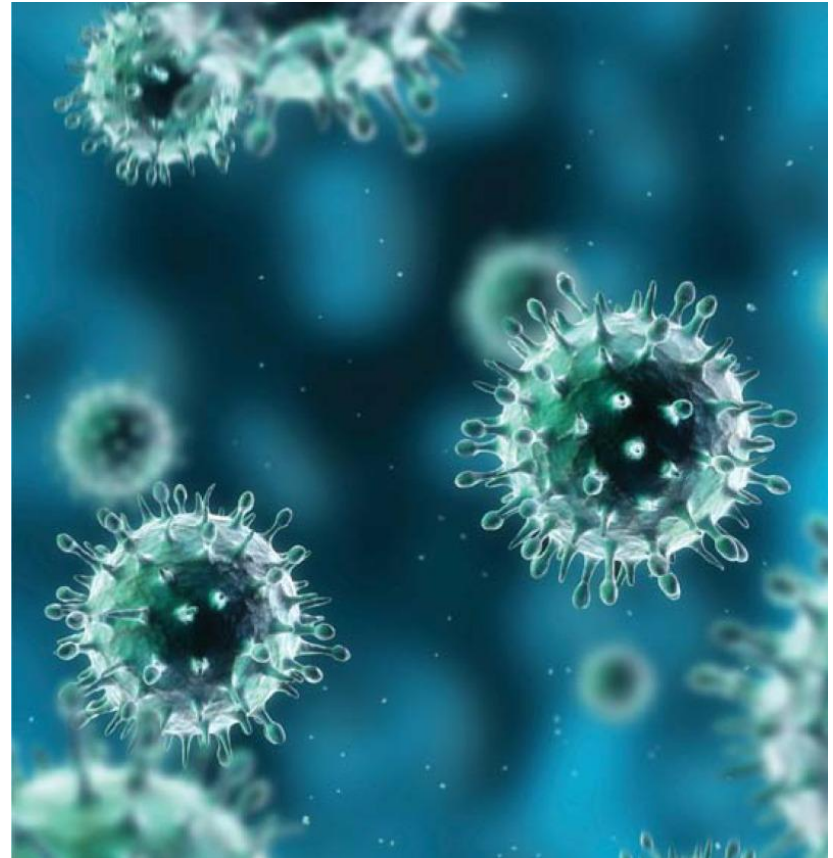
# Long COVID

- Persistent, recurring or *de novo* symptoms that can not be attributed to another diagnosis,  $\geq 4$  weeks after SARS-CoV-2 infection.

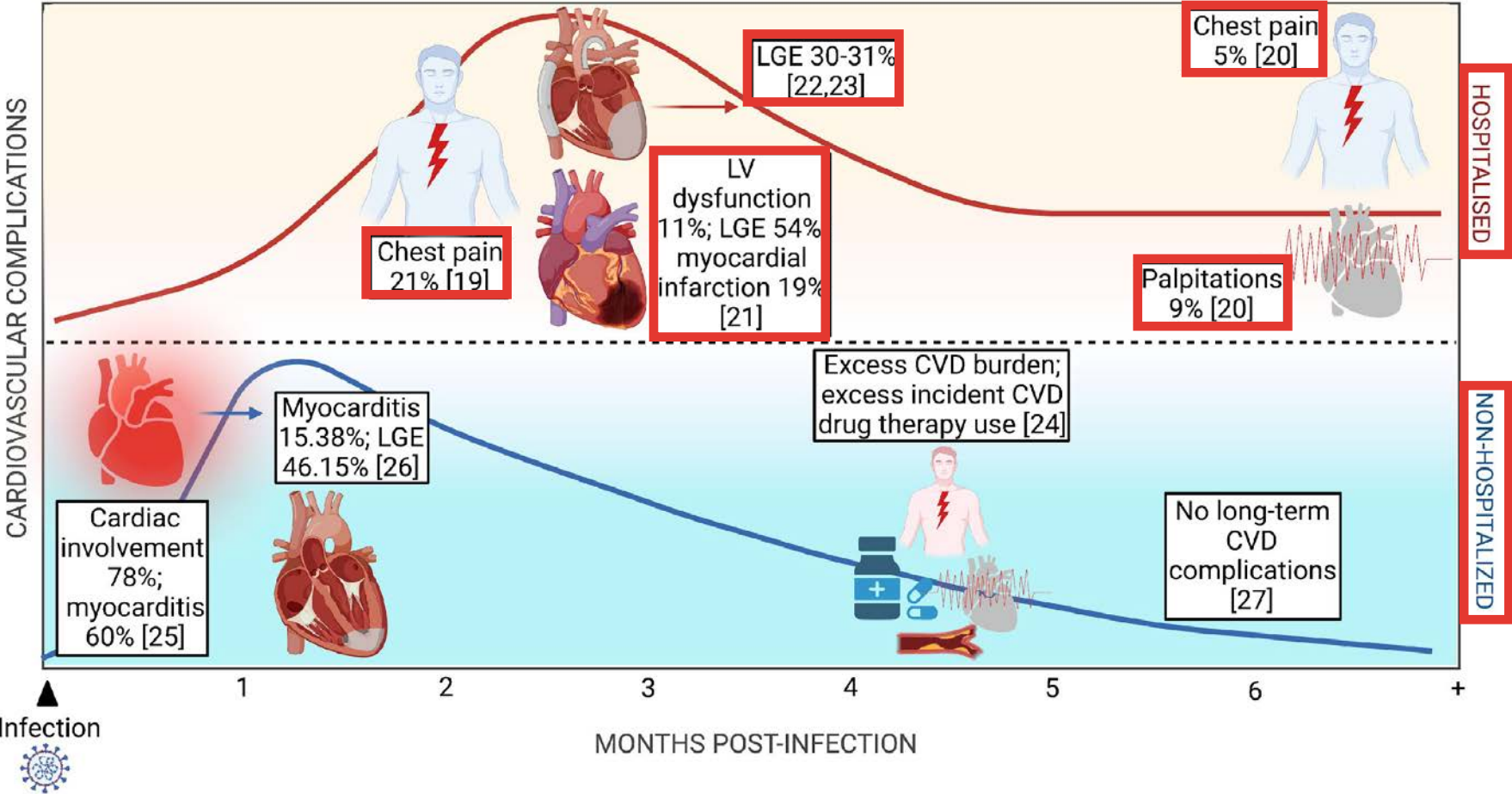
Classification	Symptoms <sup>1-3</sup>
Respiratory	<b>Shortness of breath</b> , cough
Musculoskeletal	<b>Muscle ache</b> , sore throat, abdominal pain
Digestive	Loss of appetite, nausea/vomiting, diarrhoea
Neurological	<b>Fatigue/malaise, loss of smell/taste, difficulty concentrating</b> , headache, trouble sleeping, anxiety, memory loss/confusion, depressed mood, vertigo/dizziness
Dermatological	Skin rashes

# Influenza A virus (IAV) cardiovascular complications

- IAV worsens pre-existing heart disease<sup>4</sup> and causes new injuries<sup>5-9</sup>
- IAV increases rates of endocarditis, pericarditis, tachycardia, ST changes, atrial fibrillation, ischemic heart disease, stroke<sup>10-18</sup>
- Early presentation, strong recovery profile<sup>18</sup>

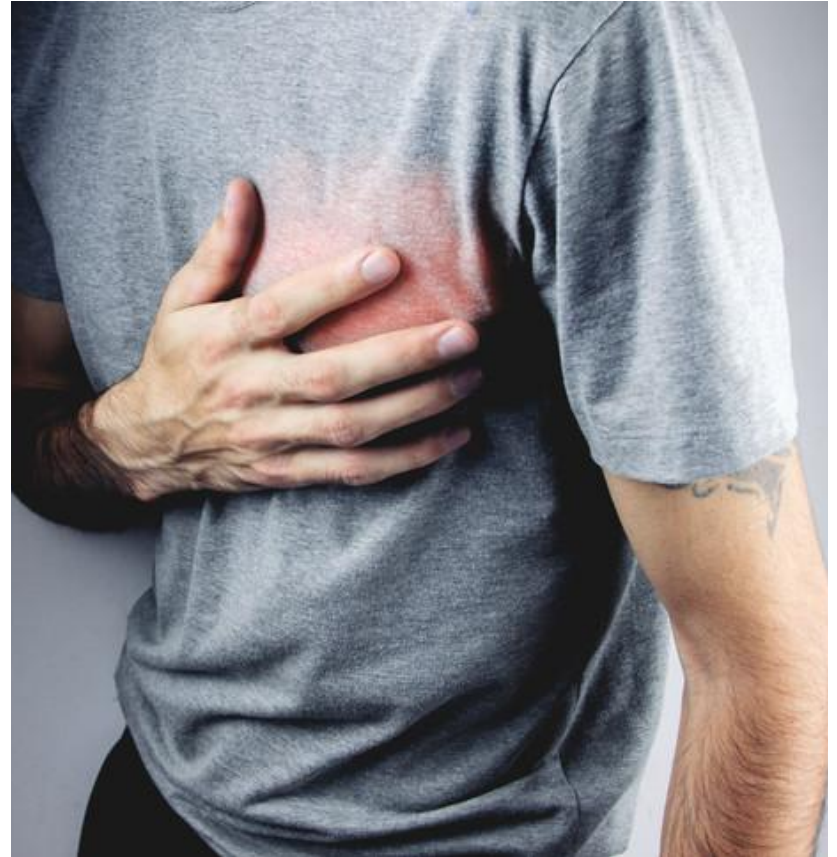


# Long COVID cardiovascular complications



# Long COVID is recurring

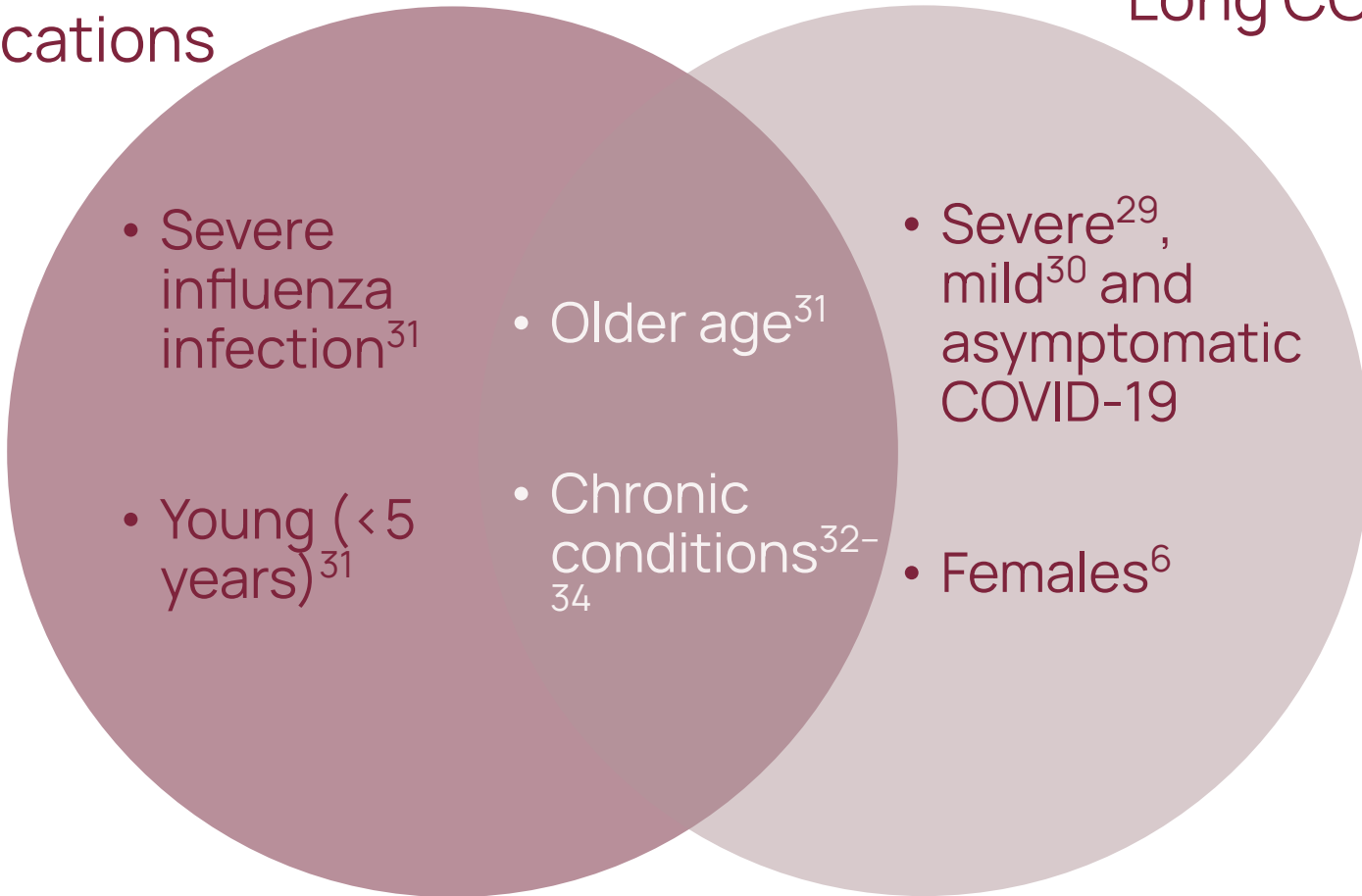
“About five weeks in I think it was for me I was still desperately short of breath, a little bit better than right at the start, but it was still coming back in massive waves. And I remembered ringing my GP from the floor on my lounge, laying on my front and kind of saying ‘I’m really short of breath, you know, do you think I should try an inhaler? Do I need to go back to A&E?’”<sup>28</sup>



# Who is most at risk?

Influenza complications

Long COVID

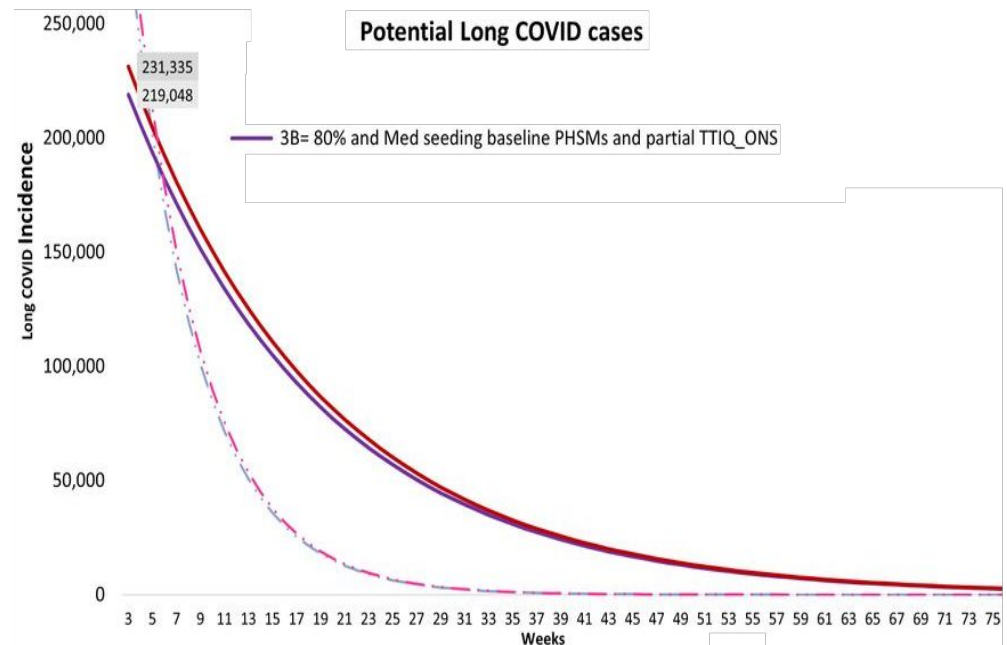


# What is the scale of the risk?

## INFLUENZA COMPLICATIONS

- 0.4-13% of adults hospitalized with influenza diagnosed with acute myocarditis<sup>35,36</sup>
- ~50,000 lab-confirmed, 'hospitalized' influenza cases per year pre-COVID-19 pandemic<sup>37</sup>
- = ~6500 people suffering from influenza-induced cardiovascular complications per year in Australia

## LONG COVID<sup>38</sup>

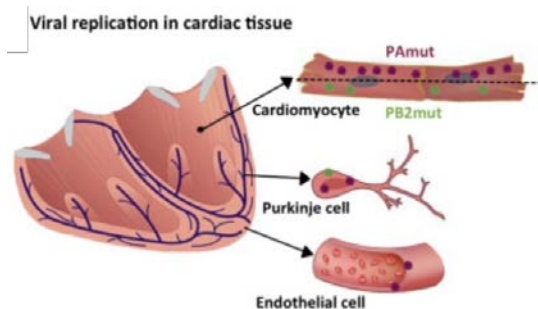




# Direct viral infection of heart

## INFLUENZA VIRUS

- IAV replicates in human induced pluripotent stem cell-derived cardiomyocytes<sup>39</sup>
- IAV and antigens found in mice<sup>40,41</sup> and human<sup>42,43</sup> hearts in small cases studies
- Only 5/624 (0.8%) of patients with acute viral myocarditis had IAV genome in cardiac samples<sup>44</sup>



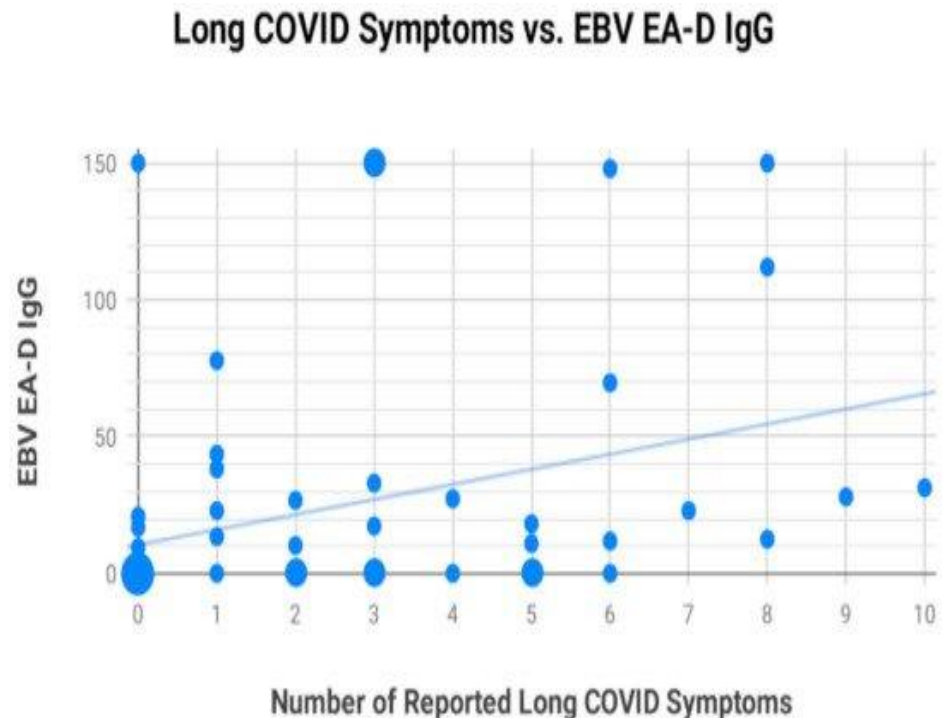
## SARS-CoV-2

- SARS-CoV-2 replicates in human induced pluripotent stem cell-derived cardiomyocytes<sup>45-48</sup> but not smooth muscle cells<sup>49</sup>
- From 39 autopsies, signs of active viral replication in myocardium of only 5 with highest viral loads<sup>50</sup>
- Viral RNA detected in 30/41 autopsied hearts but virus-positive cells rare<sup>51</sup>
- Smaller studies detected no SARS-CoV-2 in hearts of even severe myofibrillar cases<sup>52,53</sup>

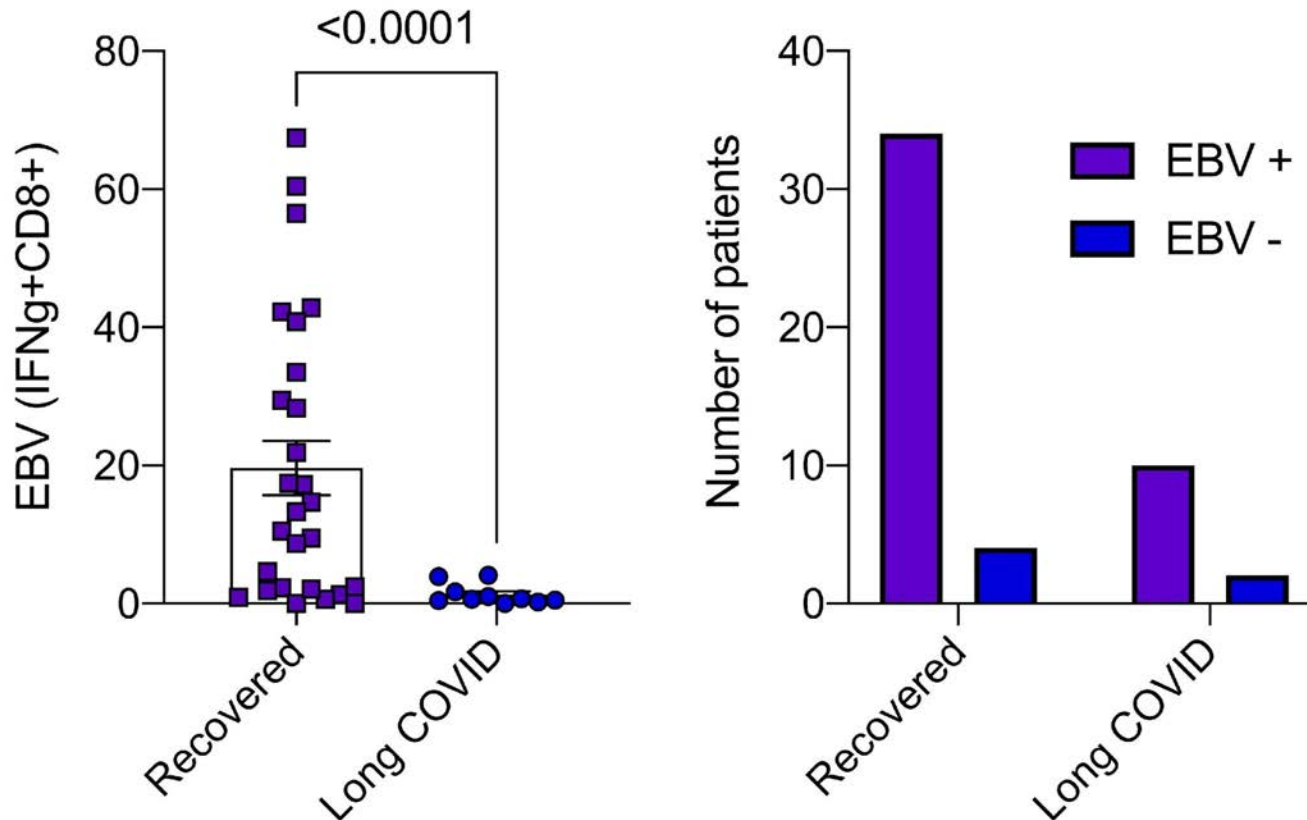


# A role for Epstein-Barr virus (EBV)

- Pathogen responsible for infectious mononucleosis<sup>54</sup>
- Continues latently in immune cells<sup>55</sup> in ~95% of adults<sup>56</sup>
- EBV can reactivate upon immunological challenge, causing symptoms similar to long COVID<sup>57</sup>
- EBV reactivated in 20/30 (66.7%) long COVID patients versus 2/20 (10%) of fully-recovered COVID-19 patients<sup>58</sup>
- Supporting studies<sup>59,60</sup>



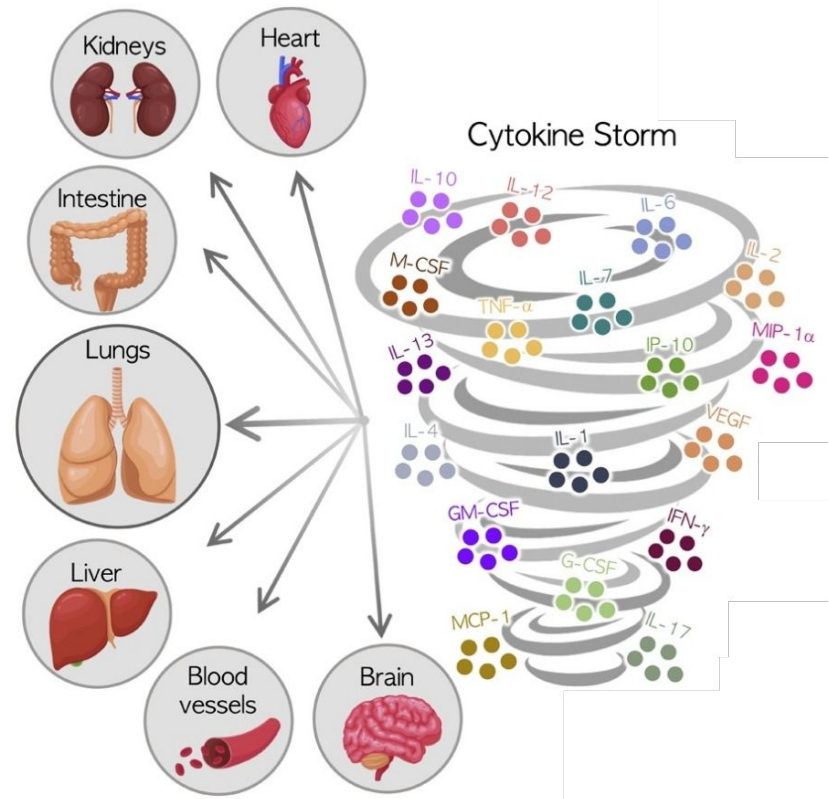
# EBV reactivation results from, rather than causes, long COVID



- EBV may contribute to some symptoms at some time-points<sup>61</sup>

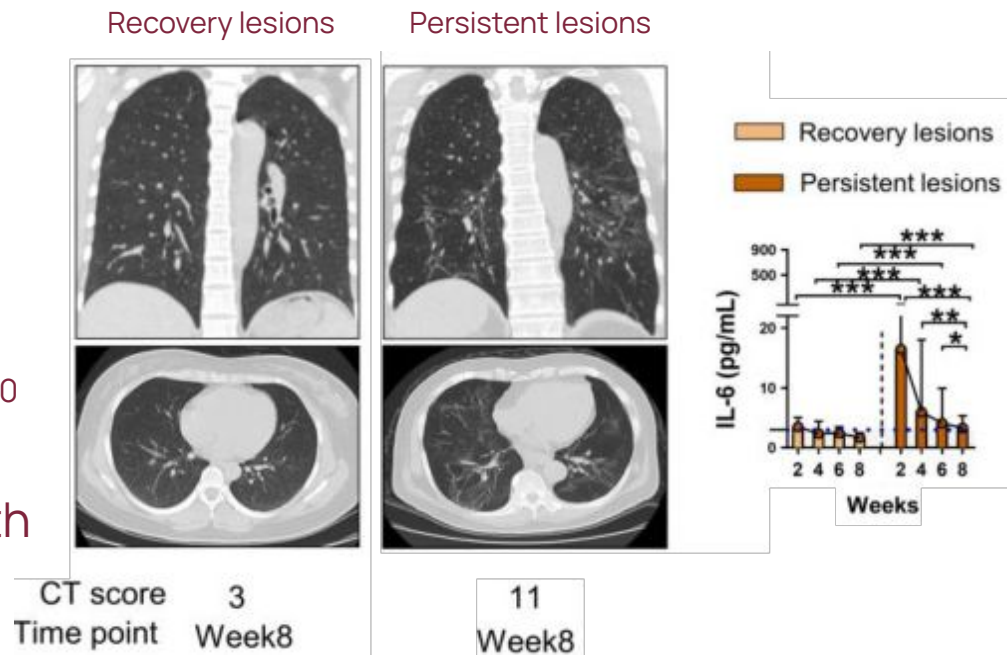
# Inflammation in acute COVID-19

- SARS-CoV-2 induces cytokine storms in severe infection<sup>62</sup>, inadvertently damaging healthy tissues
- These seem to be worse than those induced by influenza virus infection<sup>63,64</sup>
- Type I IFN dysregulation<sup>4</sup> causes greater cytokine number and variety<sup>65,66</sup>
- Inflammation more wide-spread than in influenza<sup>67,68</sup>

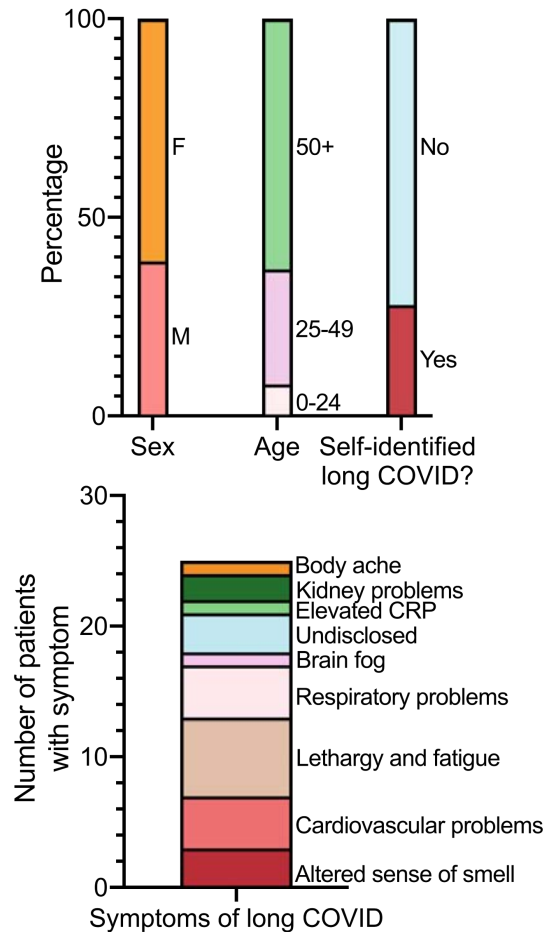


# Inflammation in long COVID

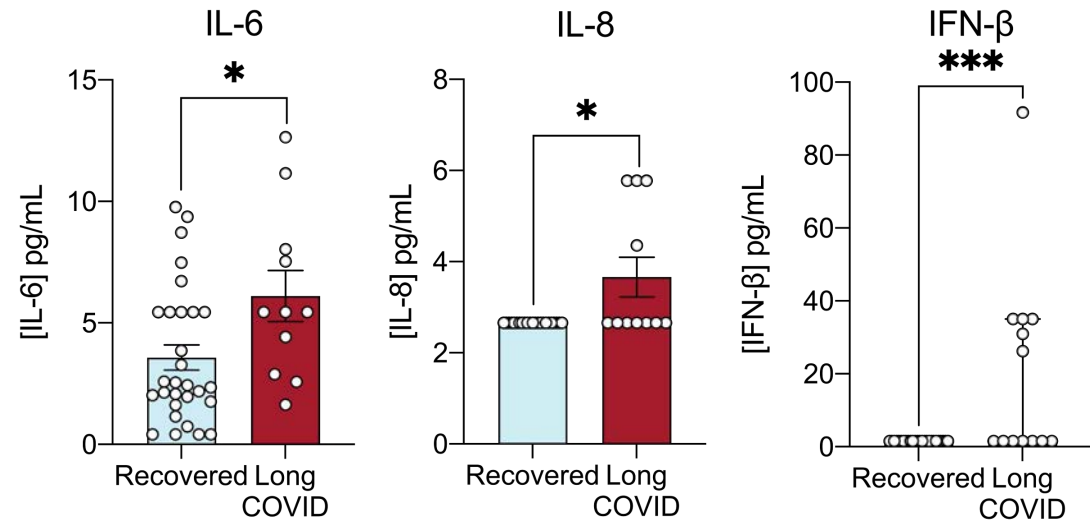
- 10% experienced persisting symptoms for >6 months, with associated MCP-1 and PDGF plasma increase<sup>69</sup>
- Long-COVID respiratory problems linked to increased plasma LCN2<sup>70</sup>
- Serum IL-6 at 4 weeks post-infection linked with chest CT score 8 weeks post-infection<sup>71</sup>
- Immunological dysfunction continued 8 months post-infection<sup>72</sup>



# Antiviral cytokines are elevated in the serum of long COVID patients 2-4 months after infection

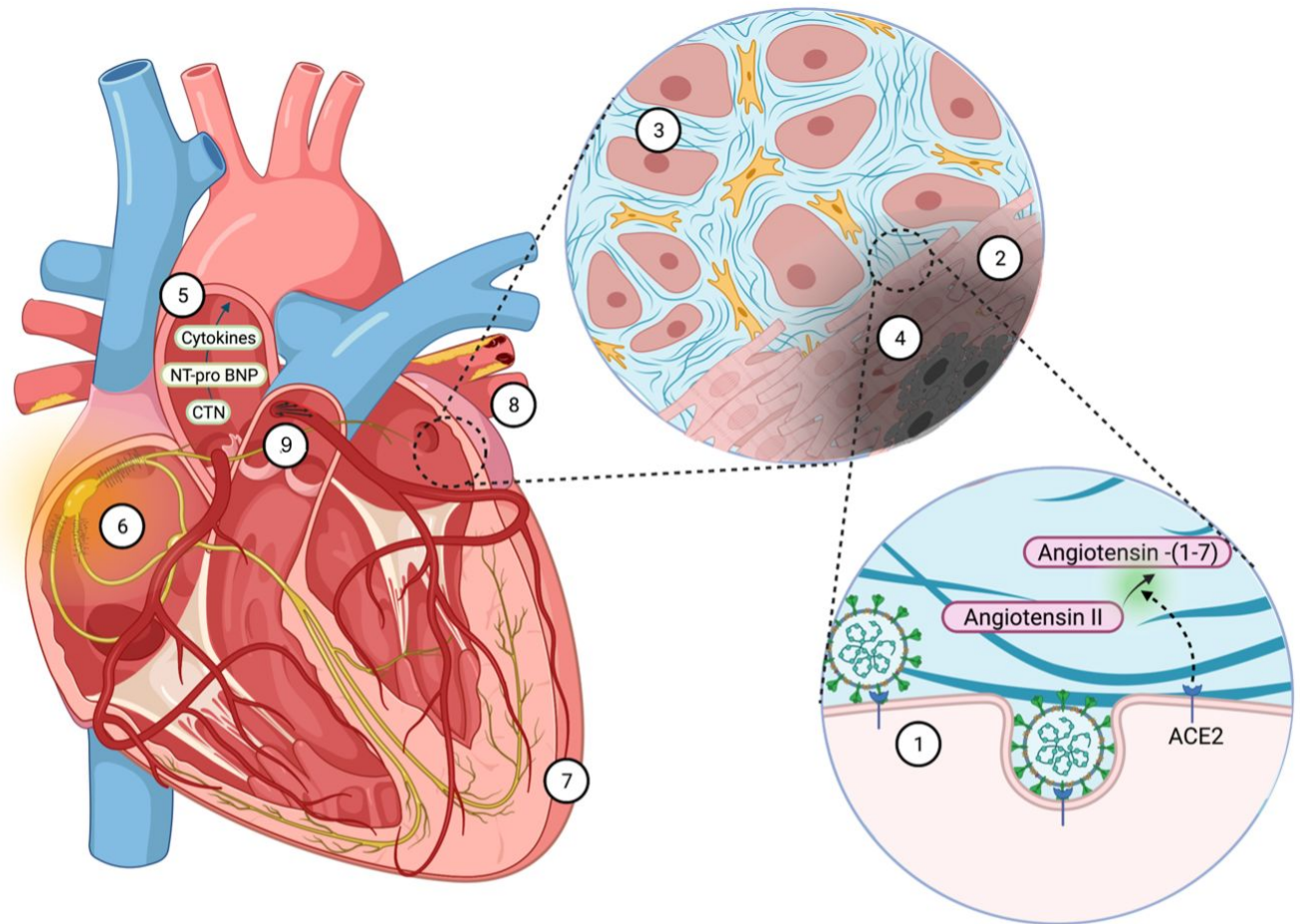


- Serum donated from recovered Australian COVID-19 patients 2-4 months after diagnosis
- Tested IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IP-10, IFN- $\lambda$ 1, IL-8, IL-12p70, IFN- $\alpha$ 2, IFN- $\lambda$ 2/3, GM-CSF, IFN- $\beta$ , IL-10, IFN- $\gamma$ .



# What does this mean for the heart?<sup>73</sup>

1. SARS-CoV-2 enters myocardium?
2. Angiotensin 1-7 ↓ + angiotensin II ↑ causes reduced coronary artery flow, myocardial ischemia and inflammation.
3. Myocardial fibrosis
4. Apoptosis
5. Elevated serum cytokines, CTN and NT-pro BNP
6. Arrhythmias
7. Compensative LV hypertrophy
8. Plaque formation
9. Increased wall shear stress

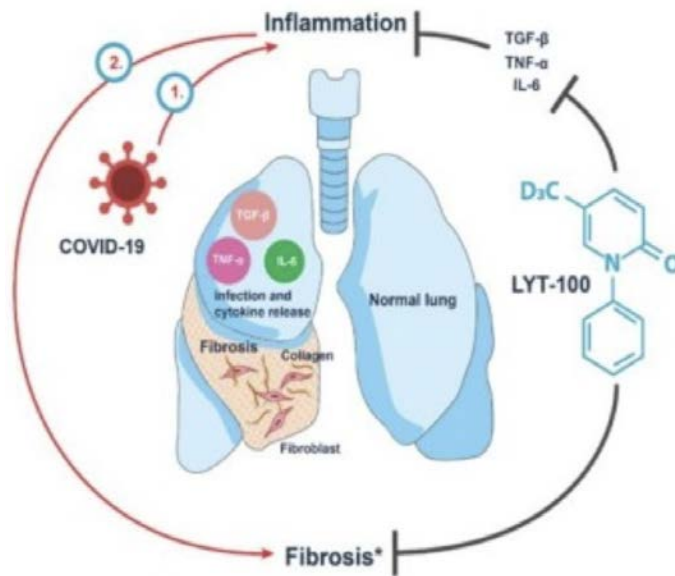




# Treatment and prevention

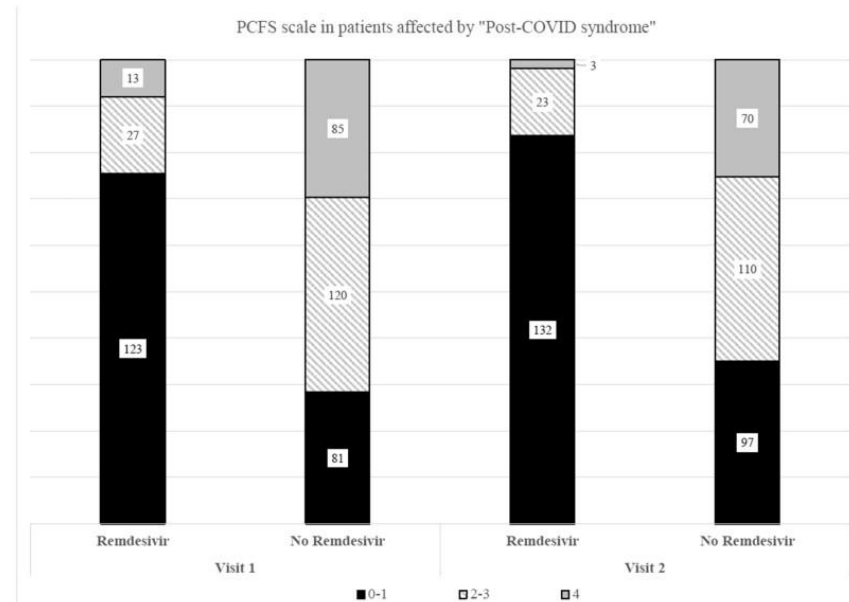
## ANTI-INFLAMMATORIES

- May cure or relieve symptoms once long COVID established
- Clinical trials for deupirfenidone<sup>74,75</sup>, statins<sup>76</sup>



## ANTI-VIRALS

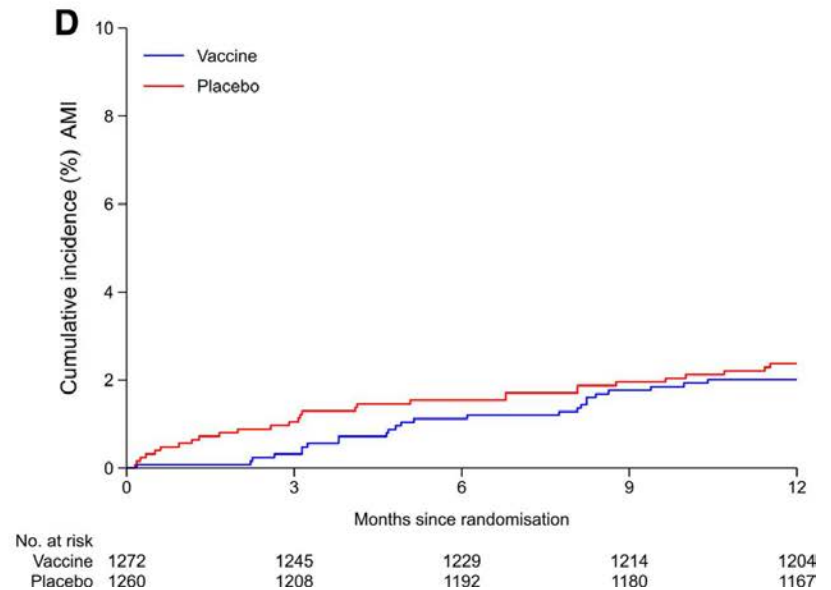
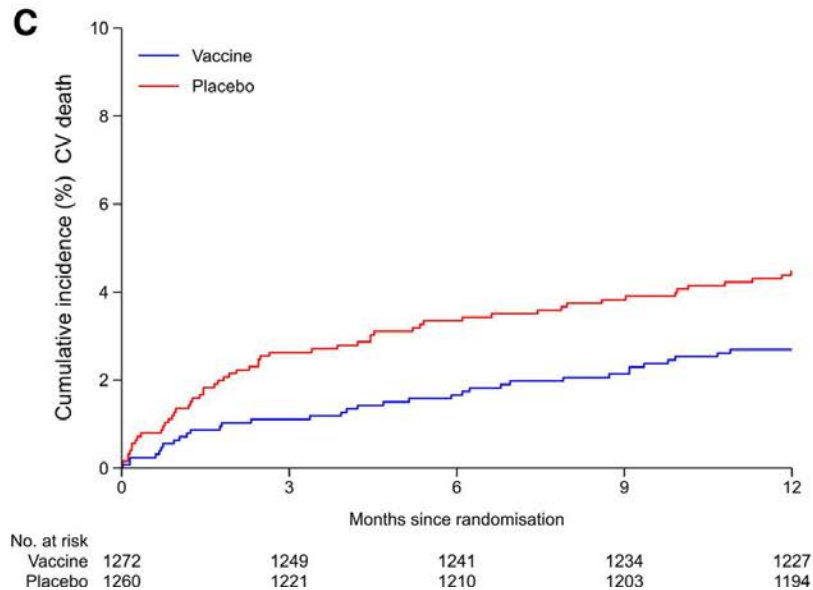
- May prevent long COVID development if given during acute infection<sup>77</sup>





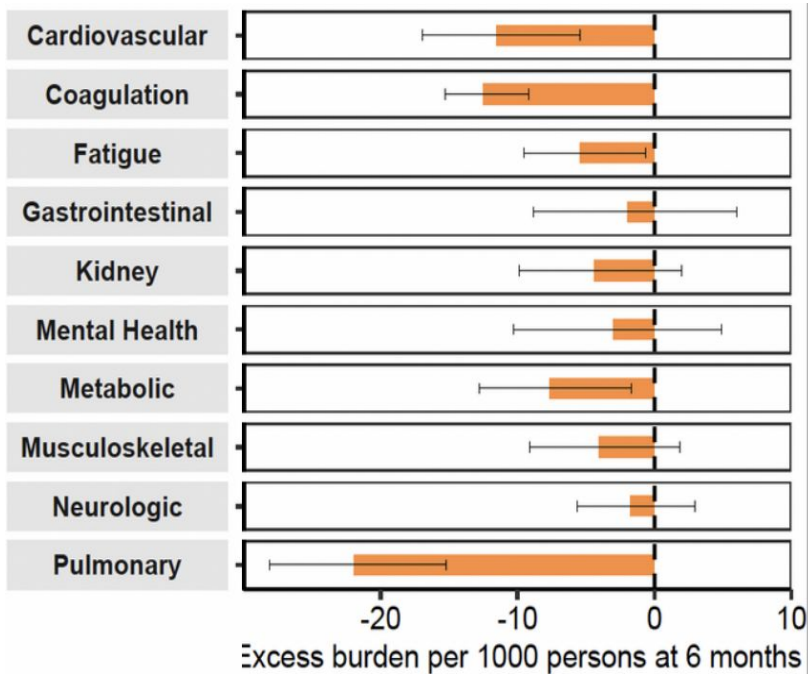
# Vaccines as prevention

- COVID-19 vaccines may prevent long COVID by allowing more targeted immune response<sup>78</sup>
- This may also be the case for influenza vaccine prevention of cardiovascular insult<sup>79</sup>



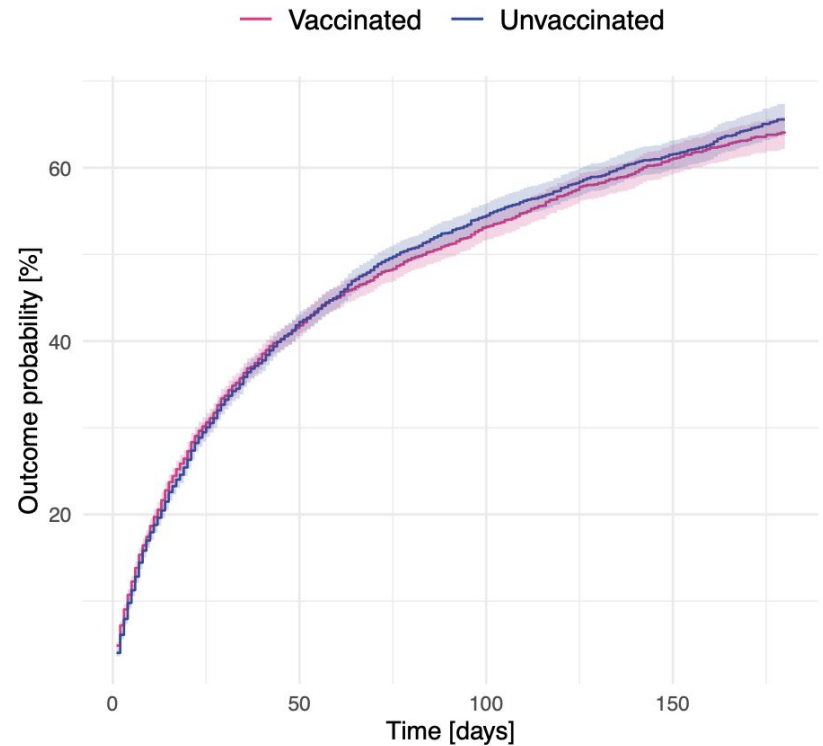
# COVID-19 vaccines as prevention

## SUCCESSFUL!<sup>80</sup>



## UNSUCCESSFUL<sup>81</sup>

Long COVID feature (any) (HR 1.01, p=0.83)



# COVID-19 vaccines as treatment

## SUCCESSFUL!<sup>82</sup>

- Analysis of medical history of 240,648 recovered COVID-19 patients
- Receiving 1<sup>st</sup> dose within 4 weeks of infection made 4-6x less likely to develop multiple long COVID symptoms
- Receiving 1<sup>st</sup> dose 4-8 weeks after infection made 3x less likely to develop multiple long COVID symptoms

## LESS SO

- 40-58% of patients who received vaccine reported symptom improvement<sup>83</sup>
- 14-18% reported deterioration<sup>84,85</sup>
- A role for specific vaccines, e.g. mRNA versus adenoviral vector vaccines?<sup>85</sup>



# Conclusions

- Long COVID presents a serious threat to the Australian healthcare system and should be factored into public health management decision-making.
- Currently, there are no reliable treatments or confirmed preventative measures, except to protect against severe SARS-CoV-2 infection.
- The benefit of indirect protection against long COVID has been sorely underrepresented in discussions of the risks and benefits of COVID-19 vaccination.

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# Thank you

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