

**第13回アレルギー疾患対策推進協議会**

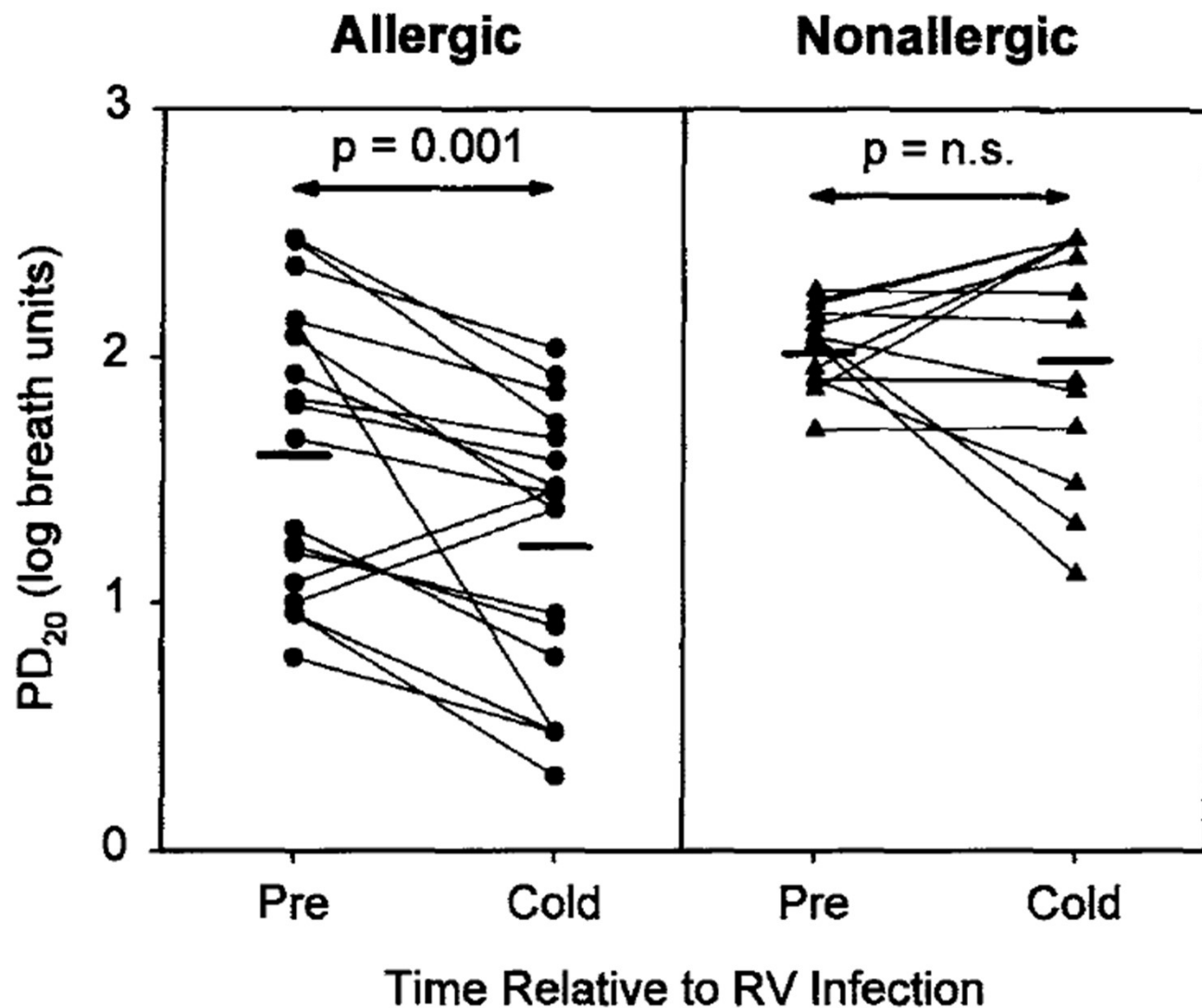
**アレルギー疾患とCOVID-19について**

**国立成育医療研究センター研究所**

**免疫アレルギー・感染研究部**

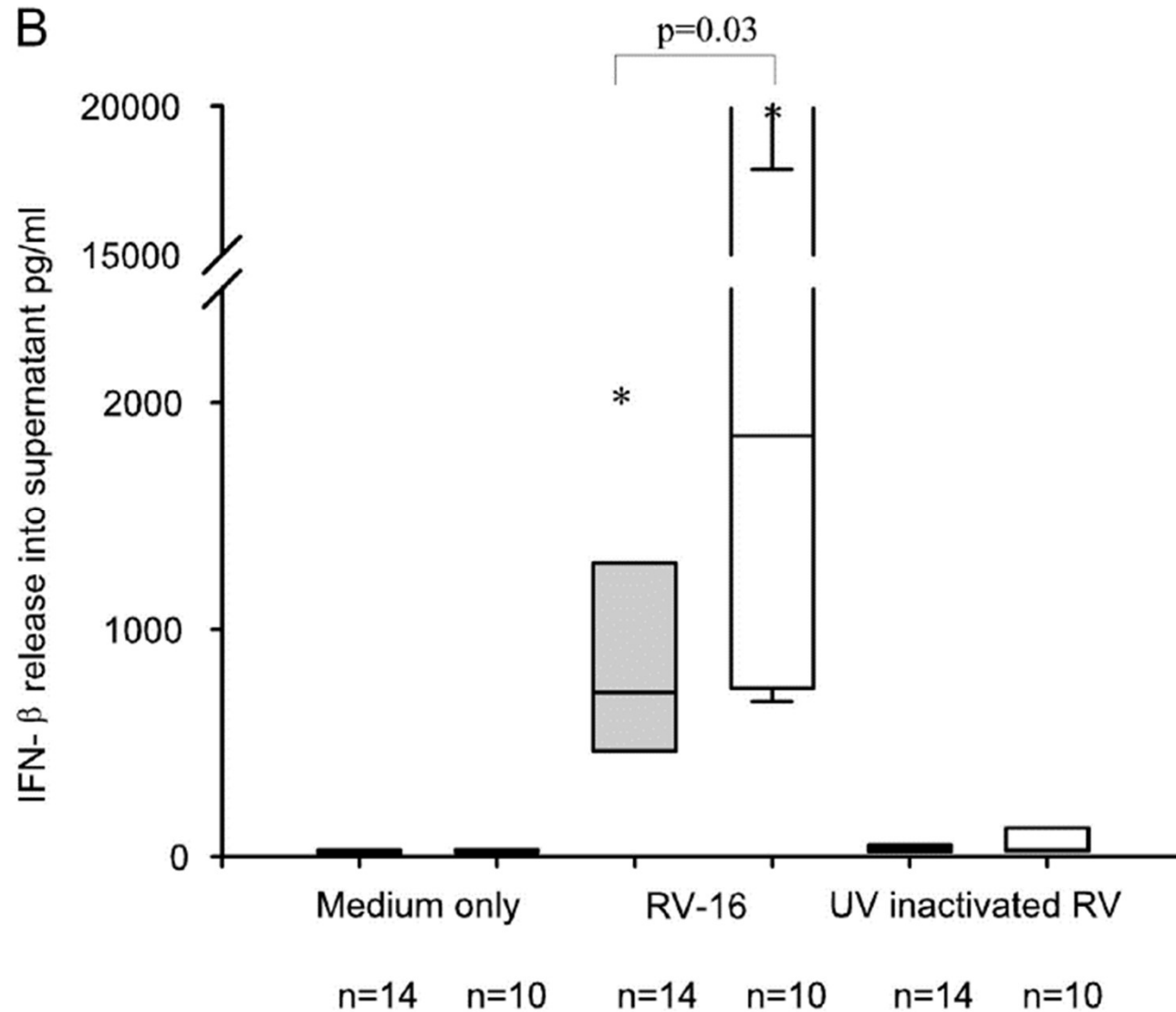
**松本健治**

# ライノウイルス（鼻かぜウイルス）の実験的感染で喘息患者だけが気道過敏性が亢進する



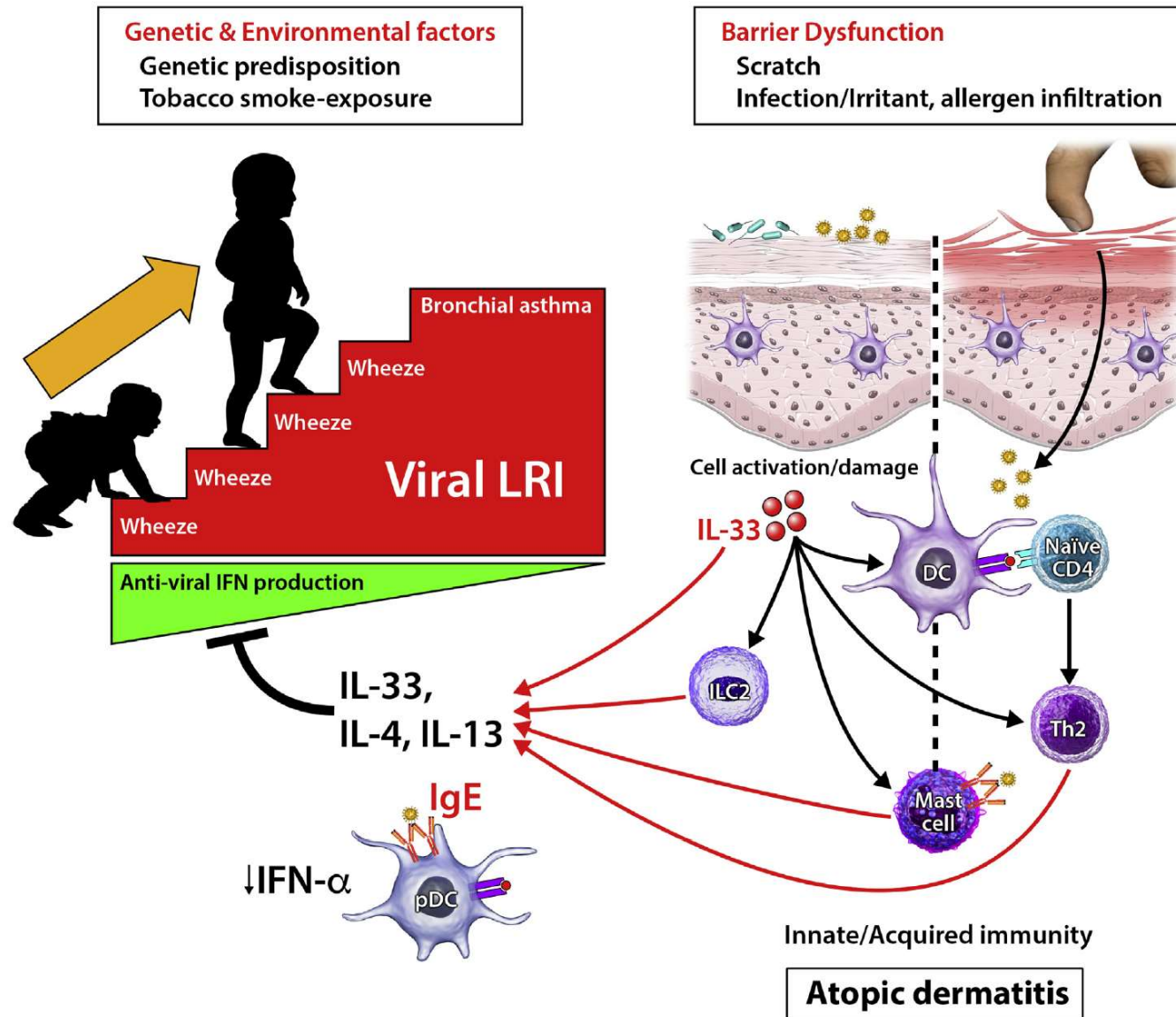
Am J Respir Crit Care Med. 1997;155:1872-6.

# 喘息患者の気管支上皮細胞はライノウイルス感染してもインターフェロンを多く作れない



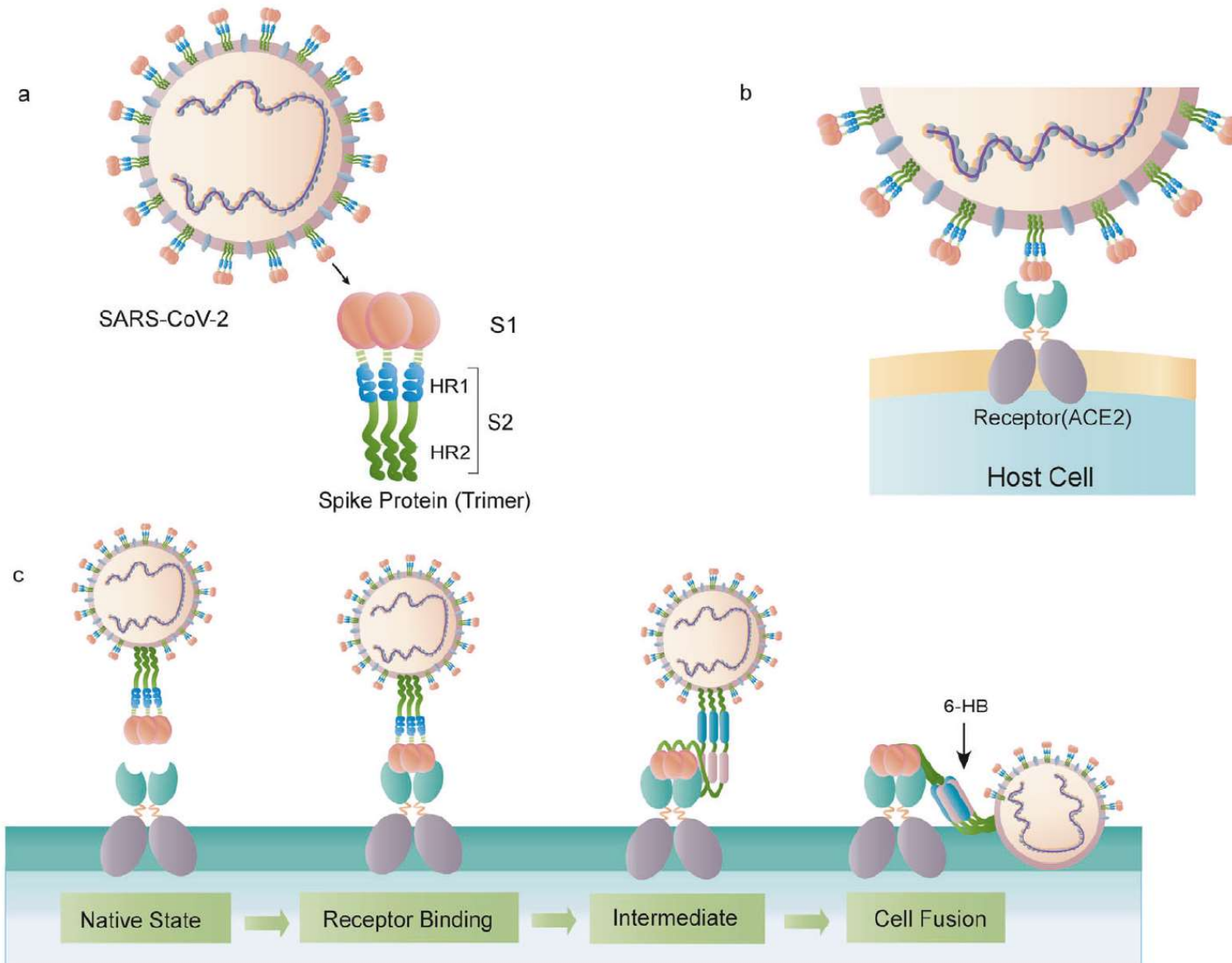
# 先行するアレルギー（アトピー性皮膚炎）がインターフェロンの産生を抑制し、乳幼児期の喘息発症を促進する

J Allergy Clin Immunol. 2020;145:1551-3.

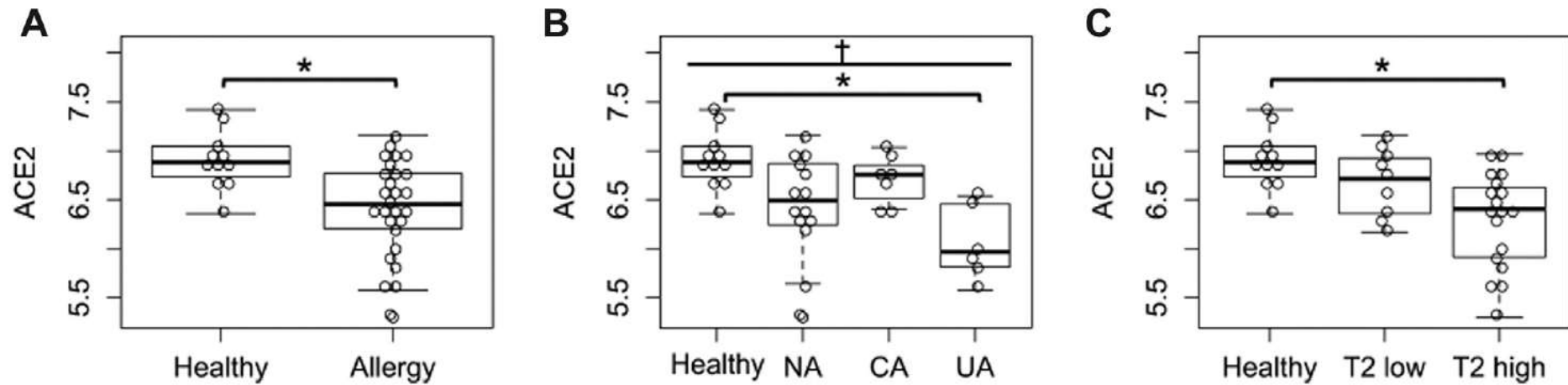


# SARS-CoV-2はACE2を介して 細胞内へ侵入する

Acta Pharmacol Sin 2020;41:1141-9.



# IgE高値となるようなアレルギー患者では鼻粘膜上のACE2の発現が減弱している



**FIG 2.** *ACE2* expression is reduced in nasal epithelial cells from type 2 (T2)-high participants with allergy. **A**, In data set GSE19187, participants with asthma and allergic rhinitis demonstrate lower expression of *ACE2*. \* $P = .0039$ . **B**, Participants with uncontrolled asthma (UA) demonstrate lower *ACE2* expression than healthy controls do. \* $P = .0053$  for the paired comparison; † $P = .0035$ . **C**, When subtyped to T2-low and T2-high groups, T2-high participants demonstrate lower *ACE2* expression than healthy controls do. \* $P = .0024$  for paired comparison. Box plots show medians with interquartile ranges. CA, Rhinitis with controlled asthma; NA, rhinitis without asthma; UA, rhinitis with uncontrolled asthma.

# 気管支喘息患者はCOVID-19に罹りやすいか

気道上皮細胞でのインターフェロンの産生が低下している

感染しやすい

ACE2の発現が低下している

感染しにくい

# COVID-19患者の基礎疾患保有率から換算すると、喘息患者はCOVID-19にかかりにくい？

TABLE I. Numbers and percentages of comorbidity in patients with COVID-19

Region	No. of COVID-19 patients	Mean or median age (y)	No. of comorbid patients (%)*			Regional asthma prevalence	Reference
			Asthma	COPD	Diabetes		
Wuhan, China	140	57	0 (0)	2 (1.4)	17 (12.1)	6.4%†	Zhang et al, 2020
Wuhan, China	548	60	5 (0.9)	17 (3.1)	83 (15.1)	6.4%†	Li et al, <sup>3</sup> 2020
Whole China	1,590	48.9	0 (0)	24 (1.5)	130 (8.2)	6.4%†	Guan et al, 2020
Georgia, USA	305	60	32 (10.5)	16 (5.2)	121 (39.7)	7.7%‡	Gold et al, 2020
California, USA	54	53.5	3 (0.6)	0 (0)	11 (20.4)	7.7%‡	Rubin et al, 2020
New York, USA	5,700	63	513 (9)	308 (5.4)	1927 (33.8)	7.7%‡	Richardson et al, 2020
New York, USA	1,651	50	99 (6)	66 (4)	248 (15.0)	7.7%‡	Singer et al, <sup>4</sup> 2020
Whole Mexico	7,497	46	270 (6)	202 (2.7)	1252 (16.7)	8.7%§	Solís et al, 2020
Total	17,485		922 (5.3)	635 (3.6)	3789 (21.6)	8.0%	

COPD, Chronic obstructive pulmonary disease.

\*The number of patients was calculated only if the total number of patients and percentages were presented.

†Regional asthma prevalence data are cited from Huang et al.

‡Regional asthma prevalence data are cited from the Centers for Disease Control and Prevention.

§Regional asthma prevalence data are cited from Solé et al.

|| $P < .0001$  by Mantel-Haenszel test.

2020年5月6日時点でのPubMedおよびGoogle Scholarで”COVID-19 x Asthma”でHitした63論文を網羅的に検索し(Systematic Review)、メタ解析した



# 喘息はCOVID-19の感染のリスクとはならない

COVID-19患者で、気管支喘息の頻度が記載されている論文19編をメタ解析した

Based on the available literature, there was no clear evidence that patients with asthma were at a higher risk of being infected or becoming severely ill with SARSCoV-2

**気管支喘息患者のCOVID-19は重症化しやすいか**

# 喘息患者が重症化するリスクは 健常者と変わらない

TABLE II. Association of asthma, COPD, and diabetes comorbidity with the severity of COVID-19

Region, country/comorbidity	Comorbidity+/- (%)			P value*
	Total	Nonsevere	Severe	
Wuhan, China†	548	279	269	
Asthma	5/543 (0.9)	2/277 (0.7)	3/266 (1.1)	.483
COPD	17/531 (3.1)	4/275 (1.4)	13/256 (4.8)	.019
Diabetes	83/465 (15.1)	31/248 (11.1)	52/217 (19.3)	.010
New York, USA‡	1651	914	737	
Asthma	99/1552 (6.0)	47/867 (5.1)	52/685 (7.1)	.128
COPD	66/1585 (4.0)	14/900 (1.5)	52/685 (7.1)	.000
Diabetes	248/1403 (15.0)	49/865 (5.4)	199/538 (27.0)	.000
Total	2199	1193	1006	
Asthma	104/2095 (4.7)	49/1144 (4.1)	55/951 (5.5)	.111
COPD	83/2116 (3.8)	18/1175 (1.5)	65/941 (6.5)	.000
Diabetes	331/1868 (15.1)	80/1113 (6.7)	251/755 (25.0)	.000

COPD, Chronic obstructive pulmonary disease.

\*P values were calculated by Fischer exact test,  $\chi^2$  test, or Mantel-Haenszel test.

†Li et al.<sup>3</sup>

‡Singer et al.<sup>4</sup>

2020年5月6日時点でのPubMedおよびGoogle Scholarで”COVID-19 x Asthma”でHitした63論文を網羅的に検索し(Systematic Review)、メタ解析した

# 喘息はCOVID-19によるICU入室のリスクとはならない

## ベルギーにおける596名の成人COVID-19患者を対象とした観察研究

TABLE V. Factors associated with intensive care unit stay due to SARS-CoV2 infection: results of the logistic regression analysis

	Simple logistic regression			Logistic regression adjusted for age and gender			Multiple logistic regression final model (N = 595)	
	N	OR (95% CI)	P value	N	OR (95% CI)	P value	OR (95% CI)	P value
Diabetes	595	2.3 (1.4-3.8)	<b>.0013</b>	595	2.1 (1.2-3.5)	<b>.0060</b>	—	—
History of cancer	595	1.7 (0.91-3.1)	.099	595	1.3 (0.69-2.5)	.40	—	—
Immunosuppressive disease	596	0.82 (0.28-2.4)	.71	596	0.73 (0.25-2.1)	.57	—	—
Hypertension	595	1.9 (1.2-3.0)	.0070	595	1.3 (0.98-2.7)	.061	—	—
Dyslipidemia	595	1.9 (1.2-3.2)	.0083	595	1.6 (0.92-2.6)	.10	—	—
Obesity	595	9.0 (4.5-15)	<b>&lt;.0001</b>	595	8.5 (5.1-14)	<b>&lt;.0001</b>	8.5 (5.1-14.1)	<b>&lt;.0001</b>
CRF	595	0.96 (0.39-2.3)	.92	595	0.82 (0.33-2.0)	.68	—	—
GOR	576	1.9 (1.04-3.4)	.036	576	1.6 (0.85-2.9)	.15	—	—
Asthma	596	1.3 (0.61-2.6)	.53	596	1.4 (0.69-3.0)	.33	1.4 (0.64-3.2)	.39
COPD	596	1.4 (0.67-3.1)	.34	596	1.1 (0.52-2.5)	.74	0.94 (0.39-2.2)	.89

# 喘息はCOVID-19による死亡のリスクとはならない

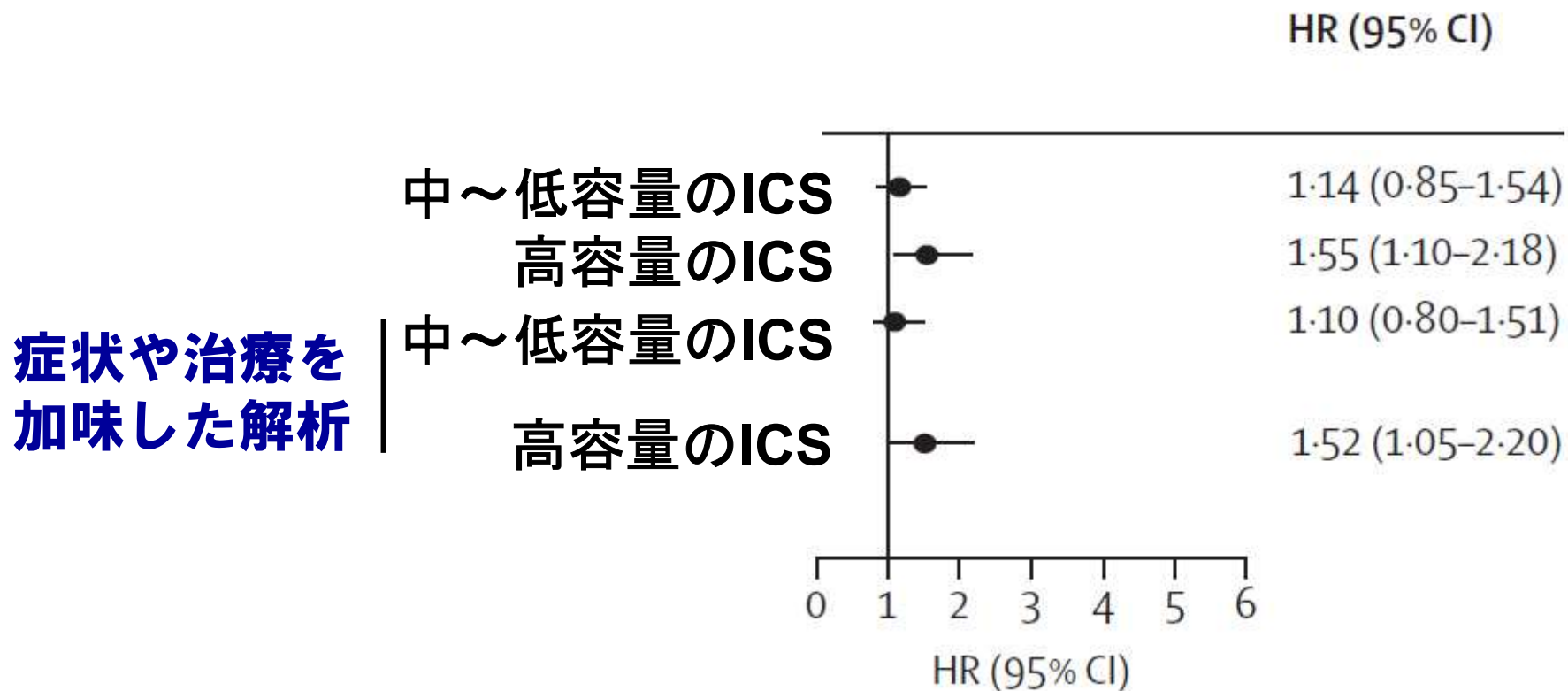
## ベルギーにおける596名の成人COVID-19患者を対象とした観察研究

TABLE VI. Factors associated with death during hospital admission due to SARS-CoV2 infection: results of the logistic regression analysis

	Simple logistic regression			Logistic regression adjusted for age and gender			Multiple logistic regression final model (N = 595)	
	N	OR (95% CI)	P value	N	OR (95% CI)	P value	OR (95% CI)	P value
Diabetes	595	2.3 (1.4-3.9)	<b>.0011</b>	595	1.8 (1.1-3.1)	<b>.031</b>	—	—
History of cancer	595	3.2 (1.8-5.7)	<b>&lt;.0001</b>	595	1.7 (0.94-3.2)	.078	—	—
Immunosuppressive disease	596	3.4 (1.6-7.2)	<b>.0020</b>	596	3.8 (1.6-8.6)	<b>.0017</b>	3.6 (1.5-8.4)	<b>.0031</b>
Hypertension	595	2.9 (1.8-4.6)	<b>&lt;.0001</b>	595	1.4 (0.80-2.3)	.25	—	—
Dyslipidemia	595	2.9 (1.8-4.6)	<b>&lt;.0001</b>	595	1.4 (0.86-2.4)	.17	—	—
Obesity	595	2.0 (1.2-3.3)	<b>.0078</b>	595	1.8 (1.1-3.2)	<b>.029</b>	—	—
CRF	595	3.7 (1.9-7.3)	<b>.0002</b>	595	2.5 (1.2-5.3)	<b>.014</b>	—	—
GOR	576	1.8 (1.004-3.2)	<b>.048</b>	576	0.86 (0.45-1.7)	.66	—	—
Asthma	596	0.41 (0.15-1.2)	.098	596	0.59 (0.20-1.8)	.35	0.74 (0.24-2.3)	.59
COPD	596	3.6 (1.9-6.9)	<b>&lt;.0001</b>	596	1.9 (0.95-3.8)	.071	1.6 (0.80-3.3)	.18

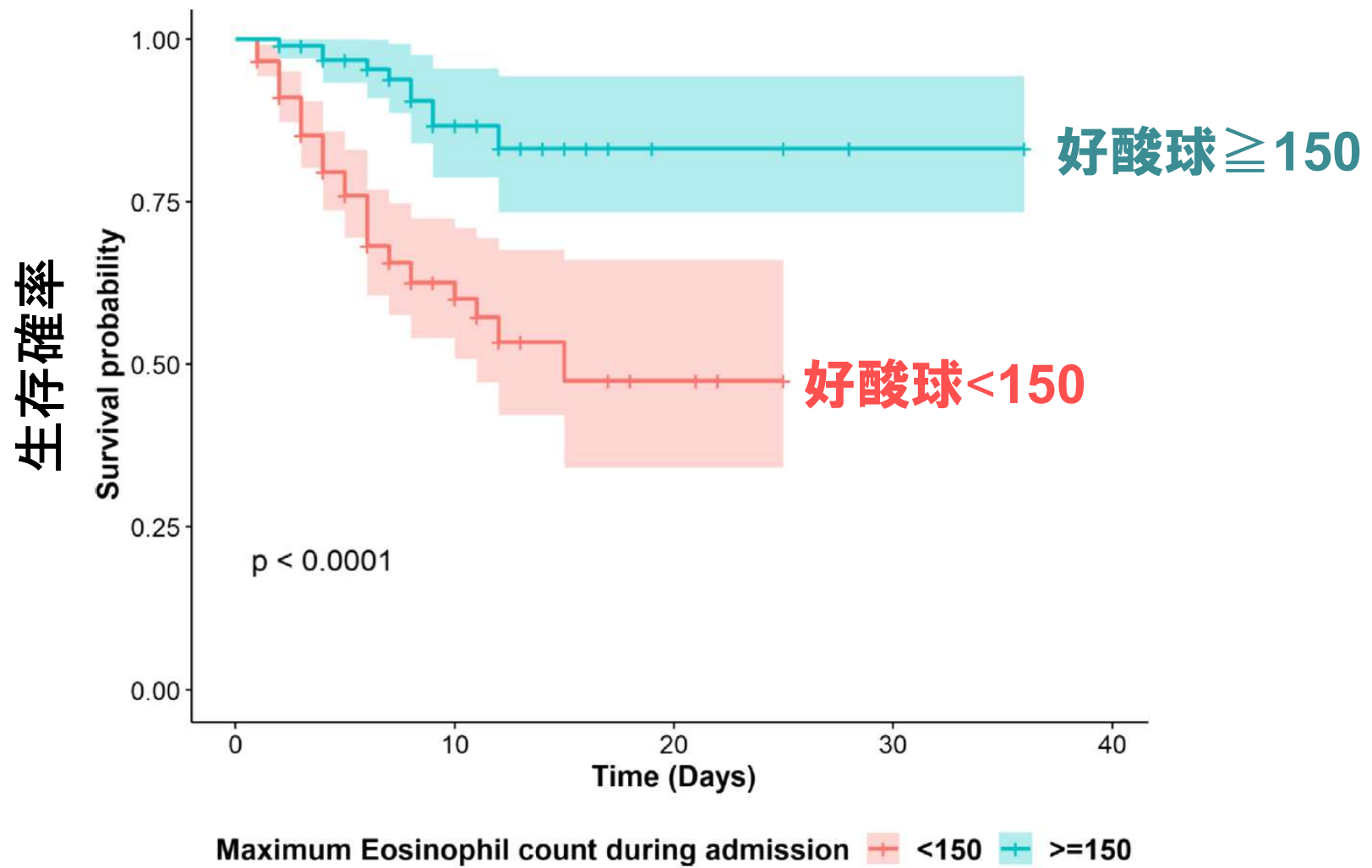
# 重症の喘息はCOVID-19による死亡の リスクとなりうる

英国の81万人の喘息患者を含む医療履歴を元に、COVID-19による死亡に与える影響について調査



Lancet Respir Med. 2020 Nov;8(11):1106-1120.

# 好酸球が少ないタイプの喘息患者は死亡のリスクが高い



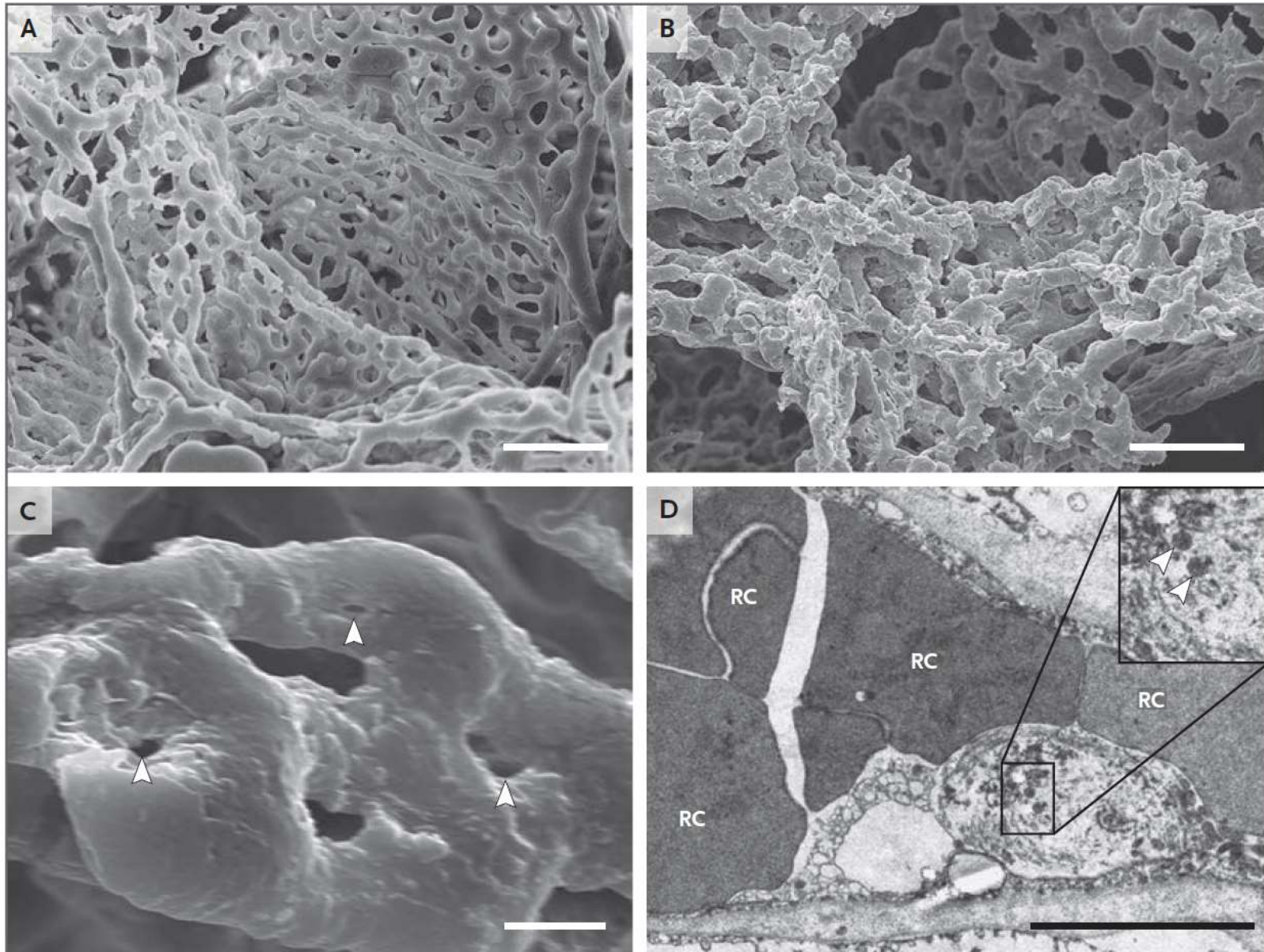
# 基礎疾患を持つ人のリスク

【年齢にかかわらず、重症化リスクが高くなる基礎疾患・状態】

- がん
- 慢性腎疾患
- 慢性閉塞性肺疾患（COPD）
- ダウン症候群
- 臓器移植による免疫不全状態（免疫システム減弱）
- 肥満（BMI：30以上）
- 妊娠
- 心不全、冠動脈疾患、心筋症などの深刻な心臓疾患
- 鎌状赤血球症
- 喫煙
- 2型糖尿病

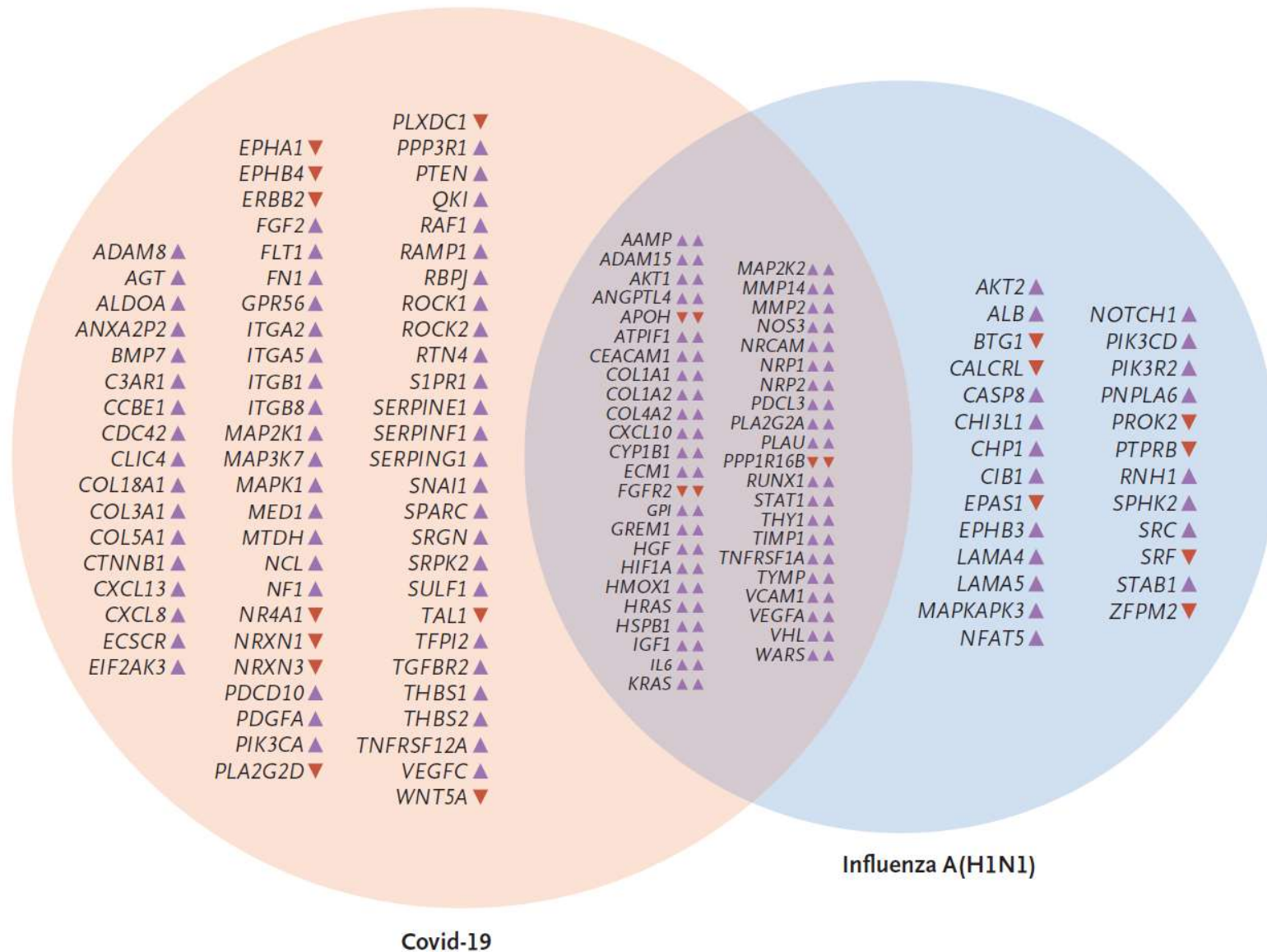


# COVID-19で亡くなった患者の肺の電顕像

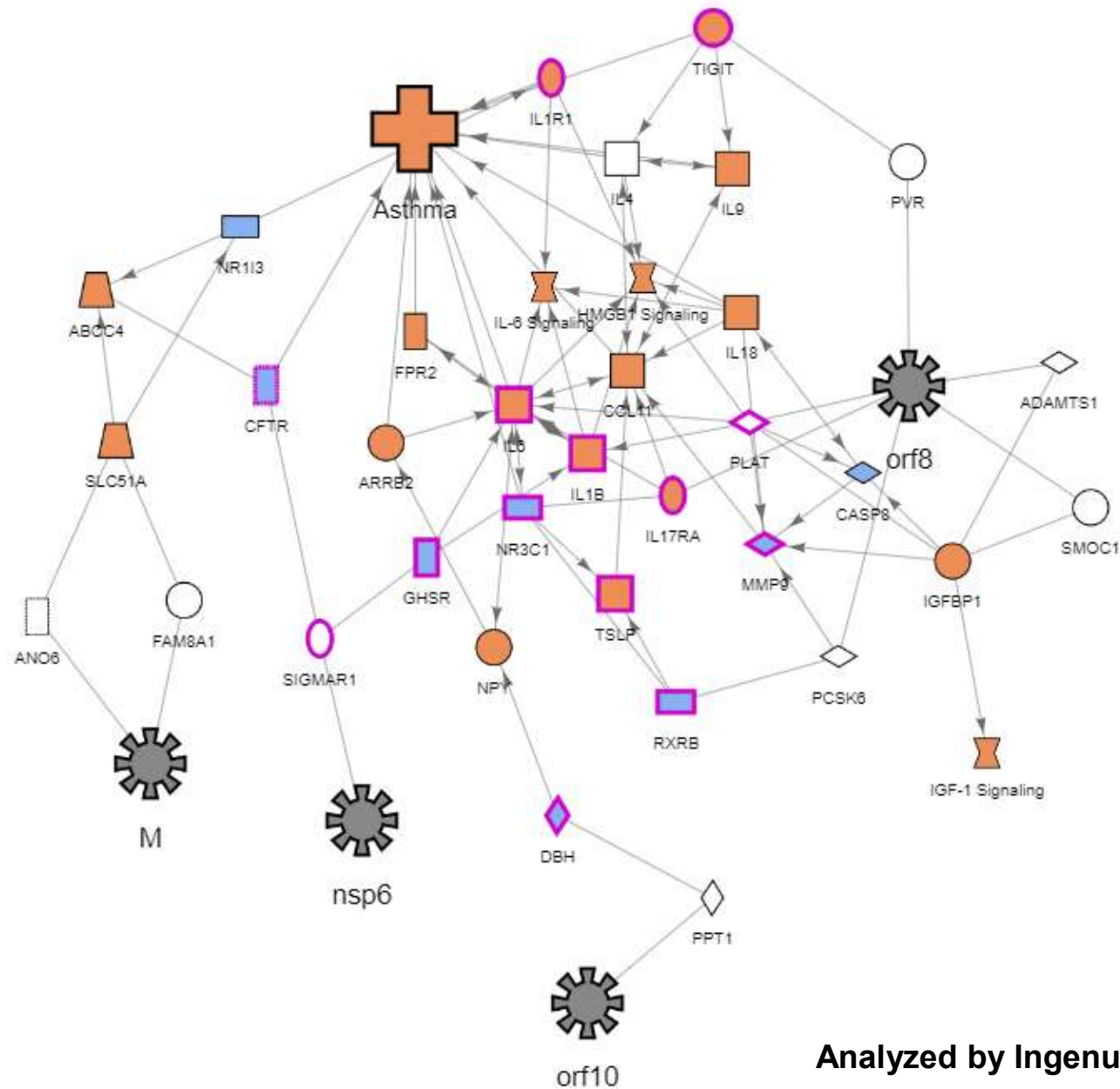


N Engl J Med. 2020 Jul 9;383(2):120-8

# COVID-19およびInfluenza A (H1N1)で亡くなった患者の肺における血管新生・炎症関連遺伝子の発現



# 喘息の悪化の分子経路にSARS CoV-2の蛋白はほとんど関与しない

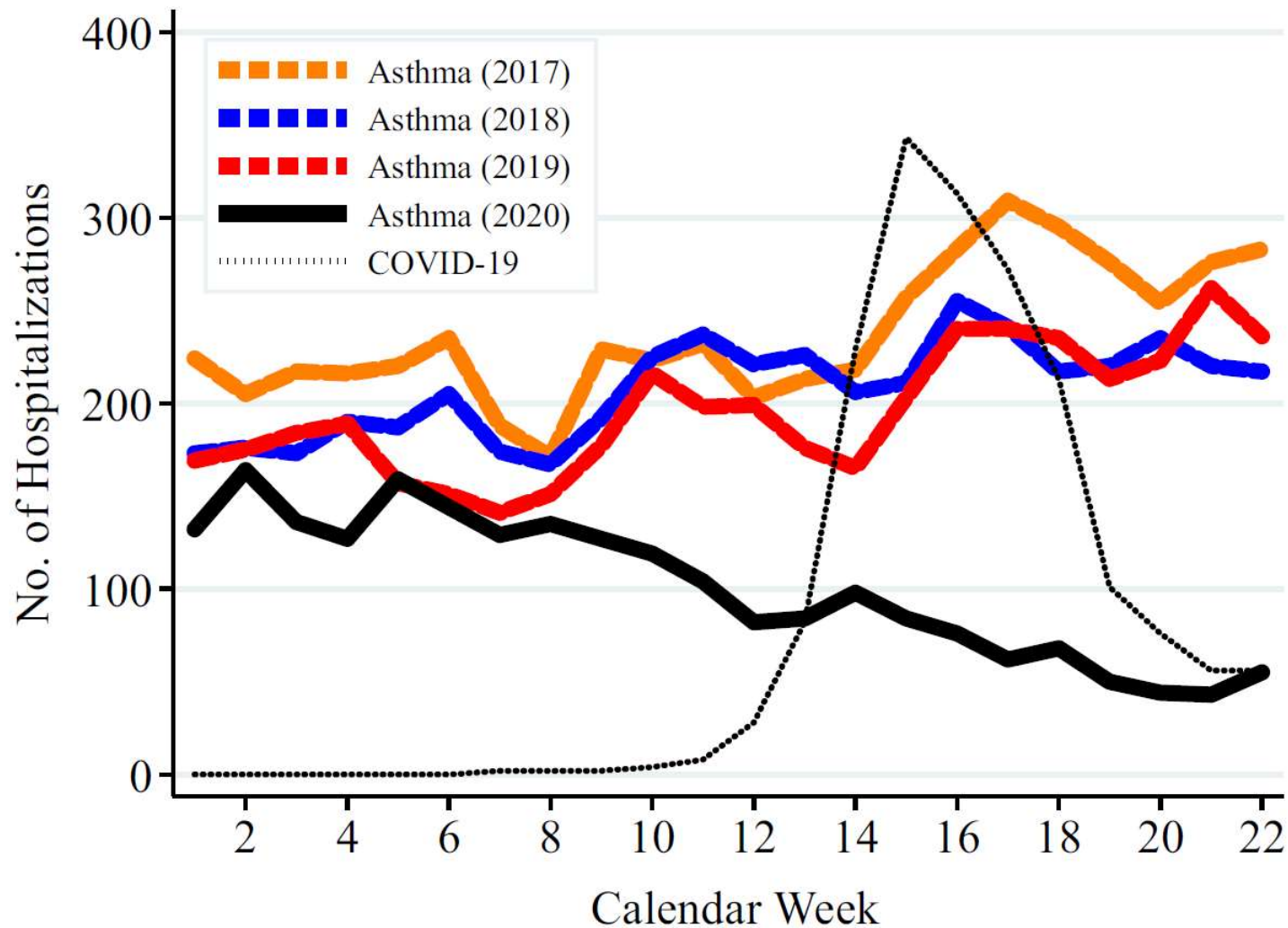


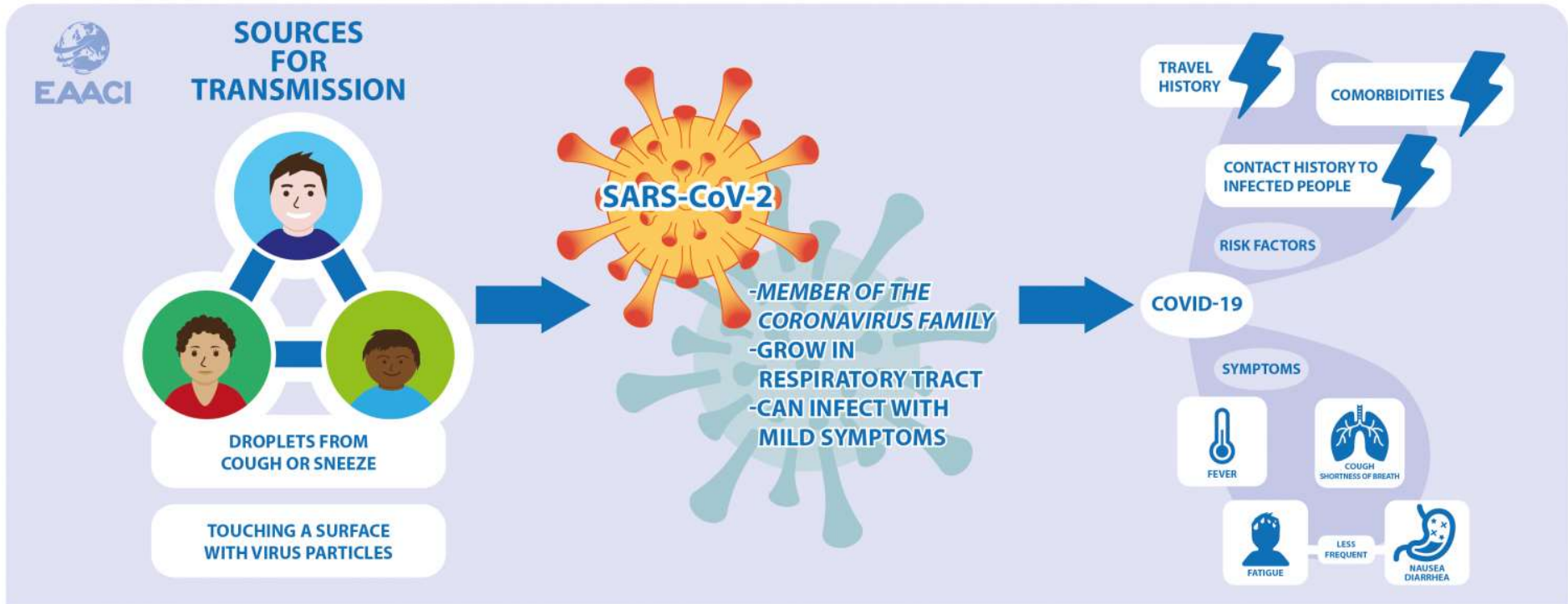
Shape Legend

- Canonical pathway
- Chemical
- Cytokine
- Disease
- Enzyme
- Function
- G - protein coupled receptor
- Growth factor
- Ion channel
- Kinase
- Ligand - dependent nuclear receptor
- Mature microRNA
- MicroRNA
- Other
- Peptidase
- Phosphatase
- Transcription regulator
- Translation regulator
- Transmembrane receptor
- Transporter
- Viral protein

Analyzed by Ingenuity Pathway Analysis software

# 本邦における気管支喘息による入院患者数の経年推移 新型コロナウイルス感染流行にあわせて減少している





**Until now, allergies are NOT a risk factor for COVID-19**

**To protect ourselves and others...**

**#STAY**

- AT HOME**
- HYGIENIC** by washing hands and cover while sneezing. Masks are for infected cases or their caregivers.
- INFORMED** and **CALM**
- AWAY FROM DROPLETS** from people who cough/sneeze.

# ワクチンによる アナフィラキシー

ファイザー社のワクチンでは

アナフィラキシーが  
47件/9943247接種  
(4.7/100万接種)

アナフィラキシーを起こした人では  
圧倒的に女性が多い(94%)

アレルギーの既往 77%  
アナフィラキシーの既往 34%

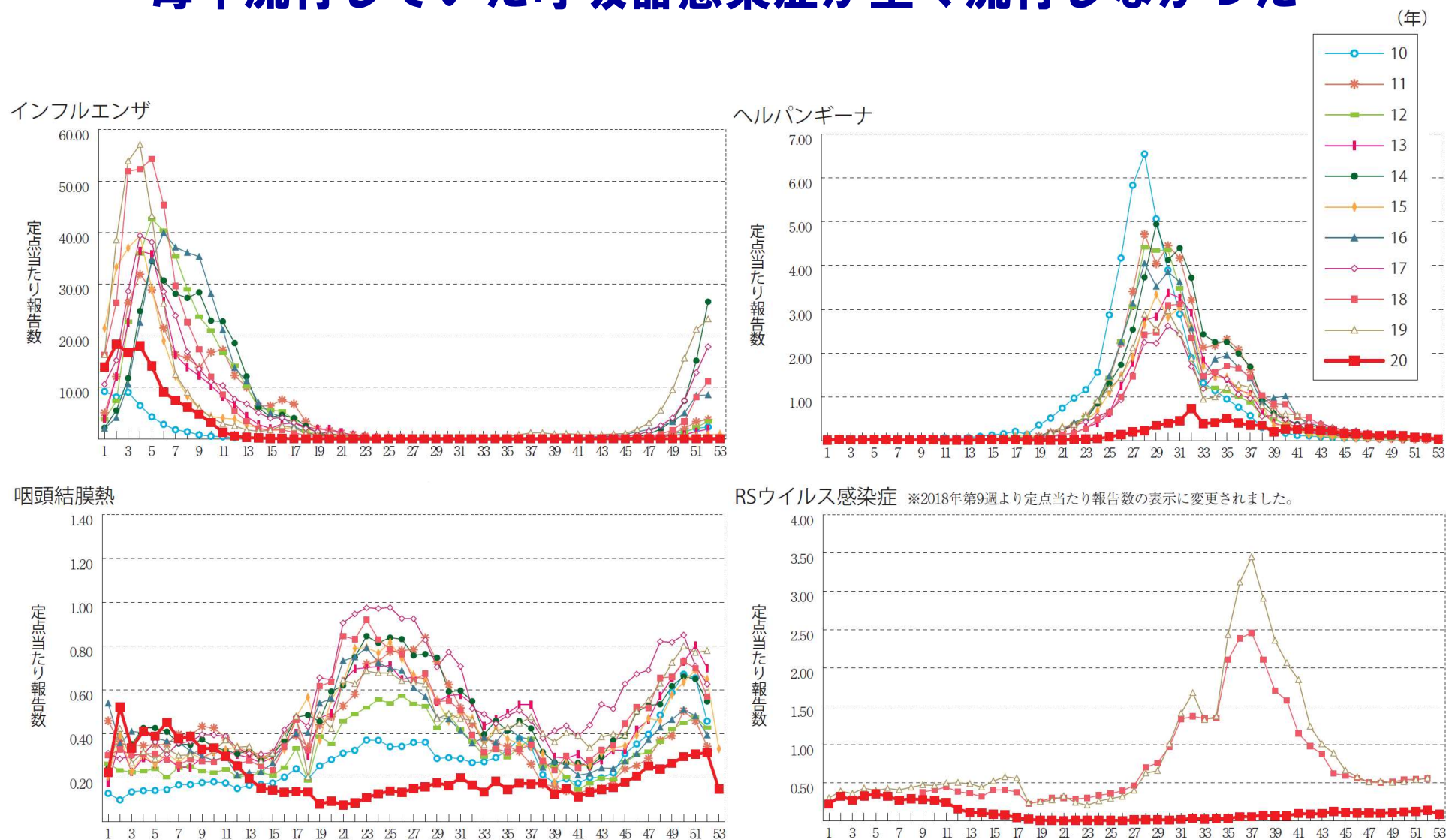
発症までの時間  
76%は15分以内  
89%は30分以内

JAMA. 2021 Feb 12. doi:  
10.1001/jama.2021.1967. Epub  
ahead of print. PMID: 33576785.

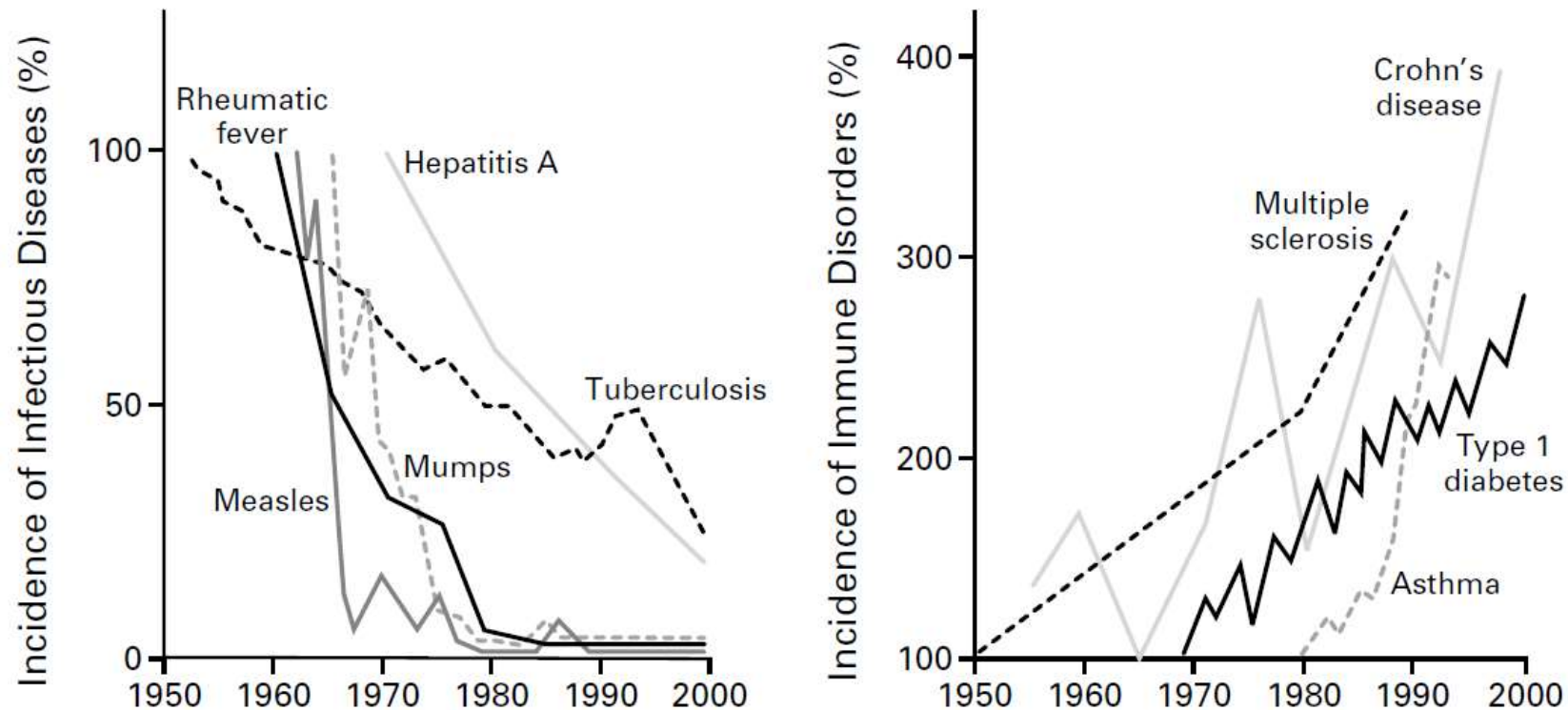
Characteristics	No. (%) of cases	
	Pfizer-BioNTech (n = 47)	Moderna (n = 19)
Age, median (range), y	39 (27-63) <sup>a</sup>	41 (24-63)
Female sex	44 (94)	19 (100)
Minutes to symptom onset, median (range)	10 (<1-1140 [19 h]) <sup>b</sup>	10 (1-45)
Symptom onset, min		
≤15	34 (76) <sup>b</sup>	16 (84)
≤30	40 (89) <sup>b</sup>	17 (89)
Reported history <sup>c</sup>		
Allergies or allergic reactions	36 (77)	16 (84)
Prior anaphylaxis	16 (34)	5 (26)
Vaccine dose		
First	37	17
Second	4	1
Unknown	6	1
Brighton Collaboration case definition level <sup>d</sup>		
1	21 (45)	10 (52)
2	23 (49)	8 (43)
3	3 (6)	1 (5)
Anaphylaxis reporting rate (cases per million doses administered)	4.7	2.5

# After COVID-19 Pandemic

## 毎年流行していた呼吸器感染症が全く流行しなかった



# 感染症の減少はアレルギーをはじめとする免疫疾患の増加と相関する（衛生仮説）



**Figure 1.** Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.<sup>12</sup> In Panel B, data on immune disorders are derived from Swarbrick et al.,<sup>10</sup> Dubois et al.,<sup>13</sup> Tuomilehto et al.,<sup>14</sup> and Pugliatti et al.<sup>15</sup>