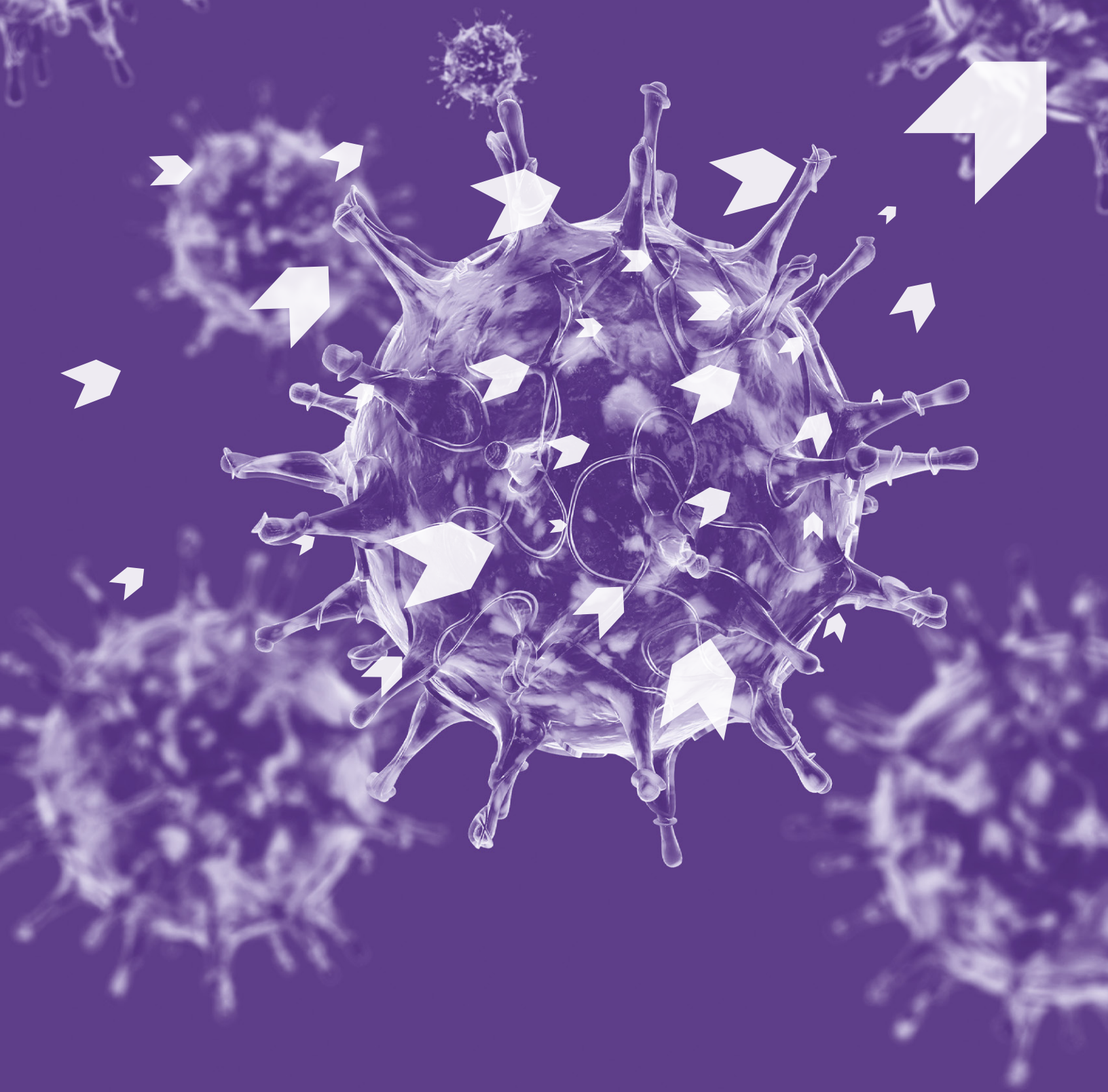

Covid-19 Report

Evaluate Vantage Team – April 2020

Evaluate Vantage

Evaluate

Foreword

Anyone thinking that 2020 might travel down a predictable path for the biopharma sector was swiftly disabused of this view in the opening weeks of the year. The coronavirus pandemic has changed the focus for almost every drug developer, whether they are working on potential treatments or trying to keep their businesses on track – or both.

The real impact on businesses has yet to be felt. Johnson & Johnson, the first big pharma company to report first-quarter earnings, said its pharmaceutical and consumer health units had a strong start to the year as patients and medical suppliers stocked up, fearing supply issues. But it was a different story in medtech, where non-urgent joint replacement procedures have been hit hard, and could fall by as much as 80% in the second quarter.

Similarly, when looking at industry data on M&A activity or venture investing, little slowdown can be seen in the first-quarter data. Deals were struck in the opening months of the year, but these had probably already been in progress when the virus struck; it is hard to imagine even the most motivated buyer initiating large and complex transactions while in lockdown.

Venture funds are flush with cash and remain motivated to fund start-ups, which will perhaps shield this particular sector; IPOs have also held up remarkably well considering the stock market meltdown. But no activity can remain unaffected by a protracted disruption, and estimates of when the world might return to normal are little more than guesses.

J&J based its guidance on a rebound starting in the third quarter, but this has to be considered best case. Some modelling studies have suggested that periods of lockdown might be required until 2022.

An effective treatment or vaccine would be a game changer, and many in biopharma are in pursuit of this goal. Collaborations between industry, academia and not-for-profits have emerged at pace: a vaccines tie-up between Sanofi and Glaxosmithkline is a remarkable example of global rivals joining forces to merge technologies and specialisms.

But despite these best efforts a vaccine will take many months to develop. Sanofi and Glaxo hope to put a candidate in the clinic by the end of this year, and launch late in 2021; J&J has selected a lead candidate, and could have first batches available early next year. Moderna is already in the clinic with its RNA-based candidate and has ambitiously claimed that a product could emerge later this year.

Therapeutics to treat the Covid-19 illness are a nearer-term hope, and Gilead's remdesivir is the biggest of these. Two large studies being conducted by medics in China have been put on hold because, with Covid-19 in the country now described as well controlled, the required subjects could not be recruited. It is thus hard to overestimate the importance of the readout of Gilead's own two trials, which have been massively upsized. Data published in mid-April on compassionate use of the antiviral raised hopes, but until rigorous trial results are available it is impossible to judge what impact remdesivir might make.

This report, a collection of previously published *Evaluate Vantage* articles, delves into what to look for in that readout. It also includes overviews of other treatments in the works, the latest thinking on various mechanisms, and a data-driven examination of the potential impact of the pandemic on the biopharma sector. A unique perspective on previous pandemics is provided, all derived from *EvaluatePharma*.

Report authors | Evaluate Vantage Team

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The quest for a cure for Covid-19

Clinical readouts do not come bigger than the data due on Gilead's remdesivir. The experimental antiviral holds the nearest hope for an effective treatment for Covid-19, the viral infection that has the world hiding indoors.

Two phase III studies being carried out in China were to have read out in April, but have just been halted owing to difficulty recruiting patients; thus the focus in on data from two upsized Gilead studies, possibly in May. Anecdotal evidence points to efficacy, but the actual level of benefit that could be meaningful remains unknown.

Showing a reduction in fever or reduced need for oxygen would be helpful; a real win would be if remdesivir helps patients leave intensive care or hospital more quickly, or reduces their need for ventilation.

It is still possible for some detail to be released however many subjects the Chinese trials managed to recruit, but any attempt to handicap the chances of Gilead's own global studies looks impossible now.

The Chinese tests, in 308 mild/moderate and 453 severe Covid-19 subjects, were quadruple-blinded and measured time to clinical recovery versus placebo. The second study is now terminated, while the first has been marked "suspended" on clinicaltrials.gov, both because "The epidemic of Covid-19 has been controlled well in China, [and] no eligible patients can be enrolled at present."

Gilead's trials, meanwhile, are continuing to enrol: the moderate disease trial is versus standard of care while the severe is uncontrolled, and they measure efficacy according to a scale from 1 (death) to 7 (hospital discharged) over 11 and 14 days respectively.

Gilead had earlier sought simply to measure hospital discharge rates at 14 days, but amended its trials' details on April 8. This might be because initial data – as both its trials are open-label it could have had access to these – were not showing much in terms of the blunt earlier metrics. The severe study also now allows subjects on ventilation.

Most importantly, the Gilead trials have been massively upscaled, increasing enrolment targets from 600 and 400 to 1,600 and 2,400. This might normally hint at fears of underpowering, but – in contrast to hospitals in China, where the outbreak is waning – Gilead has likely been hit with a surge of demand for remdesivir, and found it easy simply to add subjects to existing clinical trials. The primary completion date has been left unchanged on clinicaltrials.gov.

The Gilead studies use a 200mg loading dose followed by 100mg for nine days, and also test five-day cohorts, and seek to recruit subjects who are within four days of having had Covid-19 infection confirmed by PCR.

Remdesivir's intravenous delivery could be a drawback beyond clinical settings; other antivirals, like Roche's Tamiflu, for example, are much more effective if administered very early in the infection, and very few patients are hospitalised in the first few days of a Covid-19 infection.

Until rigorously collected data are available, remdesivir's role in this pandemic is impossible to judge. One thing seems certain: if safety is clean, even weak signals of efficacy will create huge demand.

Covid-19 study totals

Source: EvaluatePharma®; excludes observational and epidemiology studies, and patient registries. April 2020

Stage	Enrolment	Trial count
Early phase 1	1,868	4
Phase 1	2,424	10
Phase 1/2	1,069	9
Phase 2	7,413	38
Phase 2/3	9,374	21
Phase 3	44,905	39
Phase 4	12,164	16
N/A	117,013	93
Total	**196,230**	**230**

Industry-sponsored clinical studies against the new coronavirus have proliferated in the past few weeks – an analysis of data on *EvaluatePharma's* dedicated Covid-19 landing page reveals no fewer than 230 trials seeking to enrol nearly 200,000 subjects.

Commercially sponsored studies will be especially interesting to investors. This group comprises 20 trials of 17 projects, including of course Gilead's two remdesivir studies. Differences in endpoints and whether studies have a blinded control are key considerations to bear in mind here.

Also in the antiviral field is Abbvie with its anti-HIV combo Kaletra – data published in the NEJM by academic teams at several Chinese centres were considered disappointing by the authors.

Not everyone agreed: Evercore ISI's Umer Raffat pointed to subjects in whom treatment was initiated relatively quickly. In patients given Kaletra within 12 days of symptom onset, mortality was 15%, versus 27% for standard of care.

This subset comprised just 19 subjects. But it has perhaps set a benchmark for the remdesivir trials, and results from the academic sponsored Canadian study of Kaletra are keenly awaited.

Commercial projects in clinical trials for Covid-19*

Source: EvaluatePharma® April 2020

Project	Company	Study	Enrolment	Location	Design	Key efficacy measures
Remdesivir	Gilead	NCT04292730	1,600	Global	Open-label	Odds ratio for improvement at day 11 vs SOC
Remdesivir	Gilead	NCT04292899	2,400	Global	Uncontrolled	Odds ratio for improvement at day 14
Plaquenil	Sanofi	Hydra	500	US & Mexico	Quadruple-blinded	All-cause mortality vs placebo
Plaquenil (prophylaxis)	Sanofi	Phydra	400	US & Mexico	Quadruple-blinded	60-day Covid-19 infection vs placebo
Actemra	Roche	Covacta	330	?	Double-blinded	28-day clinical status vs placebo
Fludase	Ansun Biopharma	NCT03808922	250	Global	Quadruple-blinded	28-return to room air vs placebo

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Project	Company	Study	Enrolment	Location	Design	Key efficacy measures
CD24Fc	Oncoimmune	SAC-COVID	230	US	Quadruple-blinded	14-day Covid-19 status vs placebo
ASC09 + Norvir	Ascletis	NCT04261907	160	China	Open-label	Time to recovery vs Kaletra
T89	Tasly	NCT04285190	120	China	Open-label	Time to normal oxygen saturation vs placebo
Kevzara	Sanofi/ Regeneron	NCT04315298	400	US	Quadruple-blinded	% chg in CRP/time to improvement vs placebo
Kevzara	Sanofi/ Regeneron	NCT04327388	300	Europe	Quadruple-blinded	Fever resolution/15-day severity vs placebo
Kaletra	Abbvie	Solidarity	440	Canada	Open-label	29-day Covid-19 infection vs SOC
PUL-042 (prophylaxis)	Pulmotect	NCT04313023	200	?	Quadruple-blinded	14-day Covid-19 prevention vs placebo
PUL-042	Pulmotect	NCT04312997	100	US	Quadruple-blinded	14-day Covid-19 severity vs placebo
IFX-1	Inflarx	Panamo	130	Europe	Open-label	5-day chg in PaO_2/FiO_2 vs SOC
Gamifant or Anakinra	Swedish Orphan Biovitrum	NCT04324021	54	Europe	Open-label	15-day % off ventilation vs SOC
Piclidenoson	Can-Fite	NCT04333472	40	Israel	Open-label	Time to clinical recovery vs SOC
INOmax	Mallinckrodt	NONTM	20	Canada	Uncontrolled	FEV1 from baseline/QOL
mRNA-1273 (vaccine)	Moderna	NCT04283461	45	US	Uncontrolled	% seroconversion
Ad5-nCoV (vaccine)	Cansino Biologics	APICTH	108	China	Uncontrolled	Immunogenicity

* All projects therapeutic except where stated; excludes expanded-access programmes.

Among other projects, investors will also be tracking the malaria/lupus drug Plaquenil, championed by President Donald Trump. This was prompted by a highly equivocal academic trial in France; a randomised Chinese study showed no benefit.

Since the few scraps of data supporting this drug have largely been anecdotal, it is reassuring that Sanofi's studies, ending late this year, are quadruple-blinded, and one measures the tough endpoint of all-cause mortality versus placebo.

Choloroquine, the non-hydroxylated version of Plaquenil's active ingredient, is separately in a 10,000-subject Covid-19 prevention study at the UK's University of Oxford.

Another closely watched intervention is IL-6 inhibition, although the true role of this cytokine in Covid-19 remains unclear.

Roche moved to begin a phase III study of Actemra in 330 Covid-19 patients after the antibody was added to China's emergency treatment guidelines, though the company cautioned that there was very little evidence backing IL-6 inhibition in coronavirus. Sanofi and Regeneron have separately begun a trial of the similarly acting Kevzara.

One unproven theory driving this is that coronavirus infection prompts a surge in cytokines akin to that seen in response to Car-T therapy, and this causes patients to become extremely ill. Questions remain around whether this should be characterised as cytokine release syndrome; either way, clinical data are needed to figure out whether these drugs might play a role.

Other promising approaches that have yet to move into the clinic include using antibodies to target the so-called "spike" protein that the virus uses to invade human cells, or therapies based on the plasma from recovered patients. Given the level of intent signalled across the biopharma sector, the list above will soon become a lot longer.

The long path to an effective coronavirus vaccine

While efforts to develop treatments for Covid-19 continue, it will probably not be possible to declare the pandemic truly over until an effective vaccine exists. Here numerous companies are also active, and an *Evaluate Vantage* analysis reveals nearly 25 projects that should be of special interest.

Among these an mRNA vaccine has seized the early lead, courtesy of Moderna, though Johnson & Johnson's promise to develop an AAV vector-based approach on a non-profit basis might have the most promise. However, despite understandable enthusiasm, the road to having a vaccine approved is long and treacherous.

The need to build sufficient manufacturing infrastructure is just one aspect that will slow the process, and that is before a vaccine with a sufficient efficacy is developed. It could also take a while to find a product with the right mix of safety and ability to generate antibodies that offer sufficient protection.

A recent article by the Coalition for Epidemic Preparedness Innovation (CEPI) in the NEJM pointed to the industry's ability to respond quickly to the need for pandemic flu vaccines, but said those against Sars had not followed a similar path. Additionally, Covid-19 is an RNA virus, and the industry's vaccine efforts against this type of pathogen, notably RSV, have underwhelmed.

Selected vaccines in development for Covid-19

Source: WHO list, EvaluatePharma® & company statements. April 2020

Company/org	Vaccine	Type	Target	Detail
Moderna/NIAID	mRNA-1273	mRNA vaccine	SARS-CoV-2 spike protein	First clinical subjects dosed
Cansino Biologics	Ad5-nCoV	Adenovirus type 5 vaccine	SARS-CoV-2 spike protein	China study under way
Shenzhen Genoimmune	LV-SMENP-DC	Synthetic minigene vaccine	Multiple antigens	Clinical trial started Mar 2020
Inovio	INO-4800	DNA vaccine	SARS-CoV-2 spike protein	Clinical trial started Apr 2020
Oxford Biomedica/Uni of Oxford	COV001	Chimp adenovirus vaccine	SARS-CoV-2 spike protein	Clinical trial was to have started Mar 2020
Biontech/Pfizer	BNT162	mRNA vaccine	?	Clinical trial starting Apr 2020
Johnson & Johnson	?	Adenovirus type 26 vaccine	?	Clinical trial starting Sep 2020
Altimmune	AdCOVID	Undisclosed non-replicating virus	SARS-CoV-2 spike protein	Clinical trial starting Q3 2020
Emergent/Vaxart	?	Undisclosed non-replicating virus	?	Clinical trial starting H2 2020

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Company/org	Vaccine	Type	Target	Detail
Geovax	?	VLP vaccine	?	Clinical trial starting by end 2020
Arcturus	LUNAR-COV19	mRNA vaccine	?	Partnership with Duke-NUS Medical School
Sanofi	?	DNA vaccine	Viral surface proteins	Collaboration with BARDA
Translate Bio/Sanofi	?	mRNA vaccine	?	Deal signed
Dynavax/Clover/GSK	COVID-19 S-Trimer	Trimerised fusion protein	SARS-CoV-2 spike protein	Deals signed
Greffex	?	Adenovirus type 5 vaccine	?	Preparing for animal testing
Akers	?	?	Major structural proteins	Licensed candidate from Premas
Curevac	?	mRNA vaccine	?	Denies that US offered exclusive vaccine deal
AJ Vaccines	?	Protein subunit vaccine	SARS-CoV-2 spike protein	Started precelinical development
Heat Biologics	?	gp96-based vaccine	Multiple antigens/epitopes	Started precelinical development
Anges/Takara Bio	?	DNA vaccine	?	Collaboration with Osaka University
Epivax	?	Protein subunit vaccine	SARS-CoV-2 spike protein	Collaboration with Uni of Georgia
Generex/Epivax	?	Protein subunit vaccine	Multiple epitopes	To develop li-key peptide vaccines
Ibio	?	Protein subunit vaccine	?	Filed patent
Applied DNA/Takis	?	DNA vaccine	SARS-CoV-2 spike protein	Collaboration to identify candidates

It might surprise that in the coronavirus pandemic Moderna's mRNA-1273, rather than more traditional vaccine approaches, has seized early attention. One key advantage of RNA (and DNA) vaccines is that they use synthetic processes and do not require culture or fermentation, offering much faster manufacturing.

Moderna itself claims that mRNA vaccines are better at mimicking natural infection, and highlights the "agility" of its manufacturing system. Production for a phase II trial could begin in a few months, and ultimately could allow millions of doses to be made.

Pfizer, through a deal with Biontech, hopes to enter the clinic with another mRNA vaccine this month.

Three commercial vaccines are in trials at present, from Moderna, Cansino and Inovio. However, these will soon be joined by vaccines from Johnson & Johnson and the UK's University of Oxford, the latter through a consortium that includes Oxford Biomedica.

The Cepi has outlined how carrying out multiple activities simultaneously rather than linearly could curtail development times in a pandemic, and J&J says an accelerated timeline could see its lead vaccine being ready for emergency use in 2021.

That would represent an extraordinarily fast turnaround, but even so a vaccine of some sort might be needed even sooner. Thus even a suboptimal vaccine with moderate efficacy that could merely reduce the severity of Covid-19 infection might be a viable way of protecting people as next winter approaches, some think.

How the pandemic has infected biopharma

Covid-19 oils the wheels of business development

The coronavirus pandemic is clearly a major threat, but for some biotechs it represents a sizeable opportunity too. The urgent need for effective therapies to treat Covid-19 has spurred a huge number of collaborations across the biopharma sector in the past few weeks, boosting the share prices of big and small drug developers.

Transactions that might typically take months of negotiation have apparently been signed in days, and the news flow shows little sign of slowing. As such, any overview of deal making will quickly become out of date; notwithstanding this, *Evaluate Vantage* has put together a summary of the most notable announcements.

Standing out as one of the most prolific deal makers is Vir Biotechnology, a relatively young infectious disease specialist headed by George Scangos, a well-known biotech executive who previously ran Biogen and Exelixis.

For Vir the Covid-19 journey began in February with the discovery of two antibodies targeting the virus's spike protein. Next the biotech signed deals with Wuxi, Alnylam (expanded a month later), Xencor, the NIH and Biogen, variously developing antibodies, RNAi therapeutics and vaccines.

The latest deal, with Glaxosmithkline, concerns two lead MAbs against the spike protein that Vir had already identified, VIR-7831 and VIR-7832, which the partners now plan to take into phase II.

Vir's positioning as the go-to Covid-19 player is clearly allowing it to extract attractive terms: Glaxo's involvement included a $250m investment by the pharma giant, at a 10% premium, made after Vir's stock had already more than tripled year to date. The US biotech's market cap touched $3.5bn at the end of March; investors are apparently unconcerned that, at time of writing in early April, Vir's collaborations have yet to move a project into the clinic.

Among the industry's other recent coronavirus-related business development activities two deals mark an important theme: the use of plasma from patients who had had Covid-19 and recovered.

This is the focus of recent tie-ups between Xbiotech and Biobridge, and Amgen and Adaptive. Both teams are seeking to identify neutralising antibodies that the immune systems of such people had raised against Covid-19, with a view to developing these as a treatment.

Ethris and Neurimmune are pursuing a conceptually similar but practically much more difficult approach, seeking to use information gleaned from recovered patients to develop mRNA treatments that would generate the relevant antibodies once inhaled.

The list over the page is far from exhaustive, and omits the many collaborations struck between industry and both academic institutions and not-for-profits, like the Coalition for Epidemic Preparedness Innovations (CEPI).

Notable Covid-19 deals and collaborations

Source: EvaluatePharma® April 2020

Companies	Press Release
Antibody focused	
Glaxosmithkline/Vir	Deal to look at anti-Sars MAbs; $250m equity investment
Xencor/Vir	MAb discovery deal
Vir/Biogen	To collaborate on manufacturing of antibodies to treat Covid-19
Vir/WuXi	To collaborate on development of antibodies to treat Covid-19
Eli Lilly/Abcellera	To co-develop Abs
Vaccine focused	
Dynavax/Clover	Vaccine collaboration
Akers/Premas	Vaccine candidate licensing deal
Johnson & Johnson	Collaborates with Beth Israel Deaconess Medical Center on Covid-19 vaccine
Generex & Epivax	To develop li-key peptide vaccines
Applied DNA Sciences	Collaboration with Takis Biotech to identify vaccine candidates
Sanofi/Translate Bio	mRNA vaccine deal
Pfizer/Biontech	Deal to develop mRNA vaccine BNT162
Biontech/Fosun	Deal to develop mRNA vaccine BNT162 in China
Emergent Biosolutions/Noavax	Development and manufacturing vaccine collaboration
Glaxosmithkline/Clover	To collaborate on vaccine with pandemic adjuvant system
Other deals	
Xbiotech/Biobridge	Start looking at plasma from recovered patients
Amgen/Adaptive Biotechnologies	Collaborate to identify antibodies based on recovered Covid-19 patients
Ethris/Neurimmune	To develop inhaled mRNA generating antibodies, based on immune systems of recovered patients
Vir & Alnylam	Expand Covid-19 RNAi therapeutic collaboration
Iktos & SRI	Collaborate on AI technology to discover new compounds
Immunoprecise & EVQLV	AI collaboration on vaccine and antibody discovery
Kleo/Green Cross Labcell	Collaboration on NK cell combo therapy
Sorrento/Mabpharm	Collaboration on bispecific fusion protein

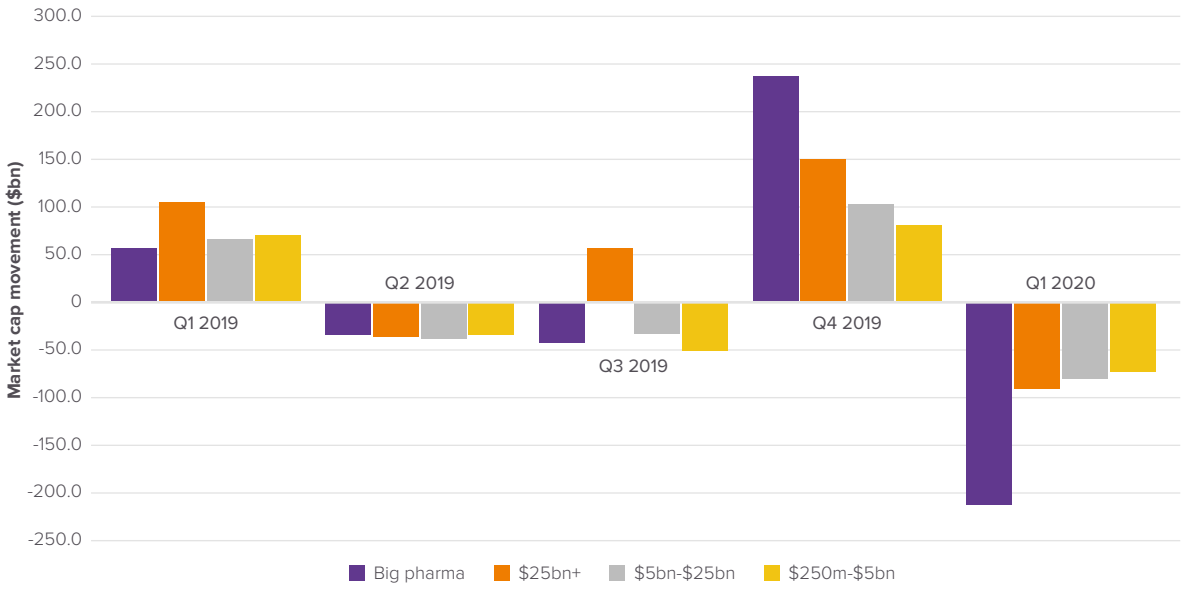
Assessing the financial harm

Measures implemented across the globe to protect populations and help healthcare systems cope have affected pretty much every aspect of life. Businesses have also been disrupted, and it is almost inevitable that companies will start reporting hits to financials in the coming months.

Pain has already been inflicted on the stock markets, of course; an *Evaluate Vantage* analysis of almost 600 global drug makers found that drug developers of every market cap bracket fell in the first quarter.

Absolute market cap gains and losses, by size bracket

Source: EvaluatePharma® April 2020



Beyond widespread share price declines, the financial damage so far has largely been restricted to withdrawing guidance for the coming year. With the first-quarter reporting season due to start towards the end of April, investors will be scouring for real dents to earnings, and estimates of future harm.

Within biopharma, certain subsectors will be hit harder than others. Those with a big primary care focus, particularly companies in the early stages of launch, could struggle to reach doctors and patients. Firms involved in elective therapies and procedures are also considered vulnerable, including cosmetic products like Botox, for example, or those involved in joint replacements.

Orthopaedics groups including Stryker and Smith & Nephew have already conceded that use of their products will fall throughout the year; the latter UK group, which is more exposed to products used in non-urgent procedures, has already put a figure on the hit. First-quarter sales will be down around 8%, while profitability will be "substantially" damaged in the second quarter, it has said.

The top five joint reconstruction companies

Source: EvaluateMedTech. April 2020

Company	Annual sales from joint reconstruction	
	2019 ($bn)	% of 2019 medtech sales
Zimmer Biomet	5.0	63%
Johnson & Johnson	3.3	13%
Stryker	3.2	22%
Smith & Nephew	1.7	34%
Wright Medical Group	0.8	88%

The pandemic might also hit another aspect of Stryker's business: its $5.4bn takeover of rival joint maker Wright Medical, currently slated to close in the second half of the year. Stryker has not indicated that it expects any problems, but after drawing the attention of the FTC the companies already looked like they might struggle to close the deal within the targeted time frame – and that was before Covid-19 hit.

Abbvie's $63bn buyout of Allergan is due to close sooner, in May. Even deals that simply need to complete paperwork could be at risk of delay, as during a global lockdown this cannot be dismissed as a mere formality.

Evaluate Vantage analysed open M&A deals in *EvaluatePharma*, and identified several healthcare-related transactions dating back to November 2018 that have been announced but have not yet been completed. Clearly not all risk being scrapped, but at the very least a delay or renegotiation are scenarios investors must now consider.

The Stryker-Wright deal seems to hold the potential for a worst-case scenario: that the pandemic leads to a lengthy delay, by the end of which the target business's valuation has shifted. Wright shares have dropped in the past couple of weeks to trade 10% below Stryker's offer price.

Selected pending acquisitions in healthcare

Source: EvaluatePharma® & company filings. April 2020

Announced	Acquirer	Target	Target's domicile	Value ($m)	Note
17-Mar-20	Arya Sciences	Immatics	Germany	350	To close Q2 2020
16-Mar-20	Acelrx	Tetraphase	US	27	Various conditions
15-Mar-20	Advanz Pharma	Correvio Pharma	Canada	76	To close Q2 2020
03-Mar-20	Thermo Fisher	Qiagen	The Netherlands	11,500	To close H1 2021
02-Mar-20	Hypera Pharma	Certain Takeda brands	C/S America	825	To close H2 2020
19-Feb-20	Meridian Bioscience	Exalenz Bioscience	Israel	49	To close Q2 2020
12-Feb-20	Dr Reddy's	Certain Wockhardt generics activities	India	259	To close by mid-2020
11-Feb-20	Ligand	North Carolina assets of Icagen	US	40	To close Apr 2020
16-Jan-20	Biontech	Neon Therapeutics	US	67	To close Q2 2020
18-Dec-19	Fujifilm	Hitachi's imaging biz	Japan	1,633	To close Jul 2020
12-Dec-19	Altaris Capital	3M's drug delivery biz	UK	650	To close H1 2020
04-Nov-19	Stryker	Wright Medical	US	5,400	H2 2020 close, but FTC raised questions
02-Oct-19	Lantheus Holdings	Progenics	US	641	Terms amended Feb 2020
25-Jun-19	Abbvie	Allergan	Ireland	63,000	To close May after antitrust divestment
18-Apr-19	Canopy Growth	Acreage Holdings	US	3,400	Open as at Apr 2020
17-Apr-19	Echo Pharmaceuticals	Samco Gold	UK	45	Reverse takeover, open as at Jan 2020
13-Nov-18	Cipla	Avenue Therapeutics	US	180	Buying remaining 67% depends on US approval of IV tramadol

Financial risks and the threat to deal making are not restricted to drug makers, of course, and at the same time the sector faces some very specific challenges. One is to protect the integrity of clinical trials in progress, to ensure that the time and money already invested is not lost.

Most drug makers have delayed the start of new trials; with populations in lockdown, hospitals no-go destinations and doctors and labs re-prioritised, the logistics required to get studies up and running have become impossible in many locations.

Sponsors are also pausing enrolment into ongoing trials, though certain cancer studies are an exception, where patients have no other alternatives.

The potential for important readouts to be delayed is the most immediate threat here, and should be a key consideration for smaller developers and their investors, particularly as access to new capital could be curtailed for some time. A bigger risk is that patients are lost to follow-up; acknowledging this, regulators have already spelled out their willingness to consider protocol amendments, design changes and alternative methods of study subject assessment.

It is the very biggest studies that have the most to lose here – namely, pivotal trials that are approaching conclusion. These represent years of research and, in many cases hundreds of millions of dollars of investment, as well as promising to deliver important new therapies to patients in need in the coming years.

In an attempt to quantify the amount of late-stage research at risk of delays or worse, *Evaluate Vantage* searched for commercially sponsored trials of pivotal-stage projects that have yet to receive US approval, and that are slated to yield results in 2020, according to the primary completion date registered on clinicaltrials.gov.

This threw up 315 phase III studies due to end this year, in 172,104 subjects. The estimated cost of running these studies is a touch over $20bn, according to *EvaluatePharma Vision* – huge sums are in play here.

Commercially sponsored pivotal trials of novel products due to read out this year

Source: EvaluatePharma Vision® April 2020

Stage	Trial count	Total enrollment	Estimated total cost of running these studies ($bn)
Active, not recruiting	147	107,248	11.75
Recruiting	168	64,856	8.45
Total	**315**	**172,104**	**20.19**

Among these feature such projects as Pfizer's *Clostridium difficile* vaccine candidate PF-06425090, whose Clover study is, with 17,525 subjects enrolled, the biggest in this analysis. A separate PF-06425090 trial, seeking to recruit 1,960, features among the top five studies reading out this year that have yet to enrol fully.

This analysis indicates that thousands of subjects are still being sought by this cohort of studies alone. And those still in need of more patients are the most at risk of extended timelines, particularly the biggest studies in this cohort, detailed below.

The biggest phase III trials that are still searching for patients, but should be getting close*

Source: EvaluatePharma Vision® April 2020

	Company	Project (setting)	Enrollment
NCT03769090	Astrazeneca	PT027 I Asthma	3,100
NCT03918629	Pfizer	PF-06425090 I Clostridium difficile-associated diarrhoea (CDAD)	1,960
NCT03518086	Eli Lilly	Mirikizumab I Ulcerative colitis	1,160
NCT03901482	Satsuma Biotech	STS101 I Migraine	1,140
NCT03902080	Urovant	Vibegron I Overactive bladder	1,088

* Assumes primary completion date is accurate. Source: clinicaltrials.gov

The table below highlights the projects in this analysis with the biggest sales potential, according to consensus sellside forecasts from *EvaluatePharma*. Several of these trials are likely to be hugely expensive to run – and the sums below do not include the cost of other studies that might be ongoing across pivotal programmes.

Remarkably, it looks like at least five near-term blockbusters are under threat: Lilly's tirzepatide, Reata's bardoxolone, Immunomedics' sacituzumab govitecan, Bristol-Myers Squibb's Tyk2 inhibitor and Galapagos's filgotinib.

Events that occurred in the days after *Evaluate Vantage* ran this analysis prove that these concerns are real. Lilly said it would pause enrolment into most ongoing studies; Galapagos took a similar step across the filgotinib programme but said the fully enrolled Selection studies should still report in the second quarter; Reata stopped the Catalyst study to protect the enrolled patients, who were considered at high risk of severe Covid-19 complications; Bristol-Myers pushed back the primary completion date on two of the studies identified but told *Evaluate Vantage* that this was unrelated to Covid-19; and Immunomedics' Ascent trial was stopped early, though while this move might have been driven by concerns over Covid-19 the data yielded enabled Immunomedics to declare the study a success in terms of efficacy.

Blockbusters under threat? Projects in this analysis with the biggest projected sales potential, and estimated trial cost

Source: EvaluatePharma Vision® April 2020

Project and trial info	Company	2024e sales ($m)	Estimated cost of running study/ies ($m)*
Tirzepatide: Surpass 3 trial in type 2 diabetes	Eli Lilly	1,619	130
Bardoxolone: Catalyst trial in PAH	Reata Pharmaceuticals	1,608	36
Sacituzumab Govitecan: Ascent trial in TNBC	Immunomedics	1,365	75
BMS-986165 (Tyk2 inhibitor): 4x psoriasis trials	Bristol-Myers Squibb	1,178	384
Filgotinib: Selection1 trial in UC	Gilead Sciences/Gilead	1,031	218
Ozanimod: 4x trials in MS, UC and Crohn's	Bristol-Myers Squibb	966	1,112
Efgartigimod: Adapt trial in myasthenia gravis	argenx	964	29
Mirikizumab: 2x trials in UC and psoriasis	Eli Lilly	848	361
AXS-05: 2x depression trials, incl. Stride-1	Axsome Therapeutics	753	46
Fintepla: 3x epilepsy trials, in Dravet and LGS	Zogenix	694	126

For study IDs, please see this article: Clinical trial delays become reality as Covid-19 risk spreads

LGS = Lennox-Gastaut syndrome; UC = ulcerative colitis; TNBC = triple negative breast cancer; PAH = pulmonary arterial hypertension.

A lot more clinical research will be put at risk the longer the pandemic continues unchecked. A further *Evaluate Vantage* analysis finds that drug developers with a stock market listing are named as the primary sponsor on 6,461 clinical trial entries, according to clinicaltrials.gov, studies that will cost around $291bn to run.

This analysis only includes trials that are yet to report, and excludes phase IV trials.

These massive investments are far from being written off, but investors must be cognisant of potential financial impact; while larger developers have more capacity to weather the storm, smaller firms could find it harder if delays mean escalating costs, and a longer wait for sales.

Sunk costs? Estimating the bill for clinical programmes

Source: EvaluatePharma Vision® April 2020

	No. of clinical trials (phase 1-3)	Estimated 2020 clinical spend ($bn)	Estimated total cost of all ongoing clinical trials ($bn)
Bristol-Myers Squibb	307	3.69	22.32
Roche	276	3.61	21.18
Novartis	319	3.14	16.98
Eli Lilly	188	2.90	13.24
Merck & Co	227	2.82	15.26
AstraZeneca	247	2.40	12.94
Johnson & Johnson	232	2.07	11.11
AbbVie	159	1.95	10.47
Novo Nordisk	60	1.85	7.91
Sanofi	128	1.80	5.98
Total incl. others	**6,461**	**60.85**	**291.37**

Note: Includes only public companies, and trials where company is lead sponsor, and only trials due to report from 2020.

EvaluatePharma Vision's R&D cost model estimates the cost of individual clinical programmes using real-world data. Company disclosed product-level spend and clinical trial patient numbers are combined to create cost per patient benchmarks by technology and therapy type. Utilising a matching algorithm these benchmarks are applied to all commercially relevant clinical trials to estimate their cost, which can then be aggregated by product to estimate the cost of development of all products.

The medtech response

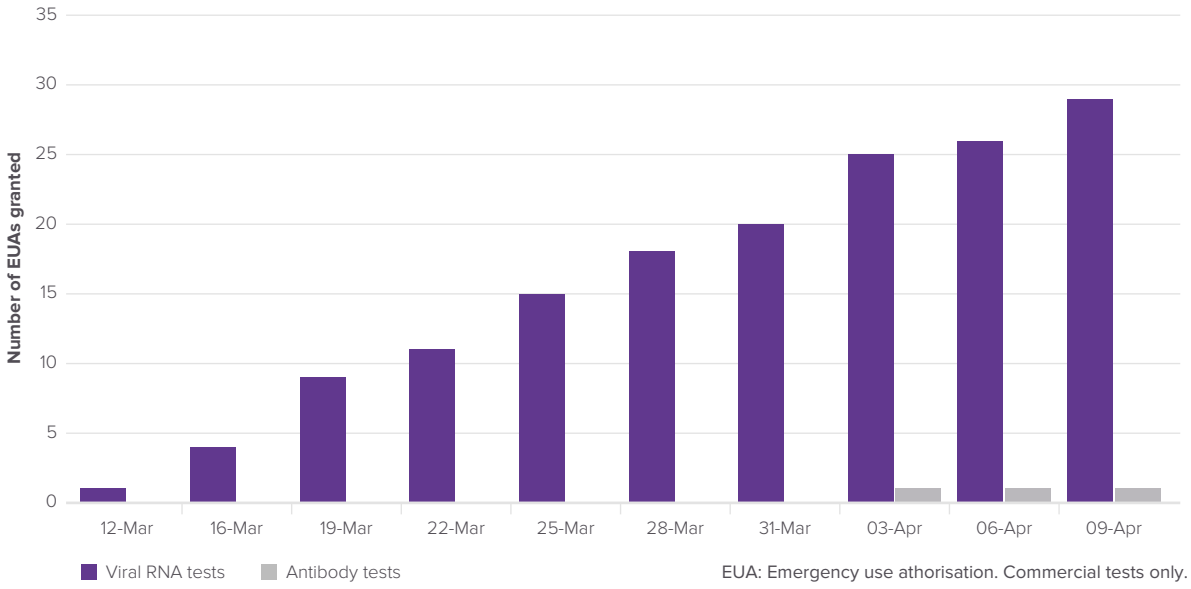
Diagnostics

Efficiently identifying people infected with the coronavirus has proved to be a major problem for almost every country. Notable exceptions include Singapore, which had experience with Sars to draw on, and Germany, which has global diagnostics groups cited domestically.

Global regulators have relaxed the rules to allow swift deployment of these genetic PCR-based diagnostics. The US FDA, for example, initially said tests had to obtain emergency use authorisation (EUA); a few weeks later this was dialled back to allow Clia-certified labs – those that have been inspected by the regulator – to begin using tests before receiving an EUA, though this would still need to be applied for.

Cumulative EUAs granted to Covid-19 tests

Source: FDA. April 2020



EUA: Emergency use athorisation. Commercial tests only.

By April 8 the US FDA had waved through 32 EUAs, to big and small diagnostics groups alike. It had also granted the first EUA to a serological or antibody test, to the small private firm Cellex; these are the so-called "game changer" diagnostics that claim to be able to detect prior coronavirus infection.

In March the FDA said serological assays could be used without its oversight provided they were clinically validated and not used as the sole method to diagnose an infection. Cellex clearly thought it was worth getting authorisation anyway – perhaps for marketing purposes.

Being able to identifying people who are likely to be immune will be hugely important in the coming months. But it is important to remember that obtaining an EUA does not amount to a determination by the FDA that a test has been proven accurate.

The poor accuracy of antibody tests is proving very problematic. The UK government found this to its cost: in early April ministers had to admit that millions of such tests had failed to produce sufficiently reliable results for widespread rollout, and the country is trying to get its money back.

Accuracy figures are not available for most of the immunoassays that have been developed, although Biomedomics has released data on a fingerstick antibody test that its partner Becton Dickinson is selling in the US. The groups claim sensitivity of 88.7% and specificity of 90.6%.

Unfortunately, if 5% of a population is truly immune, and a test with 90% sensitivity is used, its positive predictive value is 32% – meaning that 68% will yield an erroneous result. Clearly, the sort of numbers Beckton Dickinson cites are woefully inadequate, and analysts from SVB Leerink believe that to have "significant potential" tests would need to have sensitivity and specificity of more than 95%.

PCR testing is also not without its problems: finite supplies of reagents and the swabs and materials required means that capacity is struggling to keep up with demand, and of course many countries do not have the lab space available in the first place.

A substantial drop in infection rates would solve these problems, of course, which for many countries has yet to occur.

The scramble to reinvent the ventilator

The lack of mechanical ventilators to treat Covid-19 patients is a pressing problem across the world. A wide variety of efforts are being made by medtechs and non-medtech companies, regulators and academic researchers to accelerate production of approved devices, repurpose other breathing systems for emergency use, and to build new ventilators from scratch.

The engineering conglomerate Smiths Group has delayed the separation of its medtech unit, which had been scheduled for mid-year, partly so it can focus on the delivery of ventilators and other critical care devices. The company is part of the VentilatorChallengeUK alliance, from which the UK government has ordered 10,000 units.

The VentilatorChallengeUK consortium also includes Airbus, BAE Systems, Ford, Rolls-Royce, McLaren and Siemens, and is working to source and assemble parts for two ventilator designs, one of which is from Smiths Group. This device, made in the UK, is a portable ventilator usually used in ambulances and not typically used for long-term intensive care.

This consortium is only one of many deals in which engineering groups outside the medtech sector are retooling facilities to build breathing equipment. The US diversified company General Electric is working with Ford, to manufacture a simplified GE ventilator with the aim of producing 50,000 units by early July. Separately GE said it was adding manufacturing lines to its own ventilator production sites and increasing the number of shifts so the devices can be produced around the clock.

Other groups including Mercedes and Dyson are also developing their own breathing devices more or less from scratch, in collaboration with various academic groups. And Medtronic has made the design schematics of one of its ventilators available for free, to allow other manufacturers to build and release the device.

Makers of modifiable breathing devices eligible for EUAs

Source: EvaluateMedTech, FDA. April 2020

Company	No of approvals
Resmed	24
Philips	12
Fisher & Paykel Healthcare	8
Getinge	6
General Electric	6
Hill-Rom	5
Hamilton Company	5
Mindray Medical International	4
3B Medical	4
Vyaire Medical	3
Drägerwerk	3
Medtronic	3
Thornhill Medical	3
Apex Medical	3
Drive Devilbiss Healthcare	3

Note: Includes only manufacturers with at least 3 approved devices.

Even so, other initiatives will be necessary. Aware that US demand for ventilators will explode within days, the FDA is allowing breathing devices and their accessories not normally used in hospital contexts to be deployed in the fight against Covid-19.

An EUA – a temporary permission that exists as long as America is in a state of emergency – has been issued for devices including anaesthesia gas machines and positive pressure breathing devices that have been modified for use as ventilators.

The devices that are eligible for inclusion under this EUA are those that are not marketed in the US, or that are currently marketed but have been subject to an alteration that would usually need a new 510(k) clearance application.

So far EUAs have been granted to ventilators made by two Chinese companies, Beijing Aeonmed and Mindray, and by the US group Vyaire Medical.

But many other companies could benefit, as shown by the table above, which summarises the companies with the most US approvals of the kinds of respiratory devices now eligible for emergency authorisation, once they have been modified to work as ventilators.

Historical precedents

The Covid-19 outbreak has highlighted the need for effective broad-spectrum antivirals that can be stockpiled for times of need. None of the existing crop of antivirals used to treat flu are effective in treating the illness sweeping the globe, and a look at historic sales of these agents shows how use spiked during previous outbreaks.

Still, products reserved for emergency use are rarely an attractive prospect for profit-driven drug makers, and government contracts are typically awarded to fund such drugs' development. One beneficiary of these, Biocryst, which originated peramivir, said in early March that it was working with the US government to figure out whether its investigational antiviral galidesivir might have activity against Covid-19.

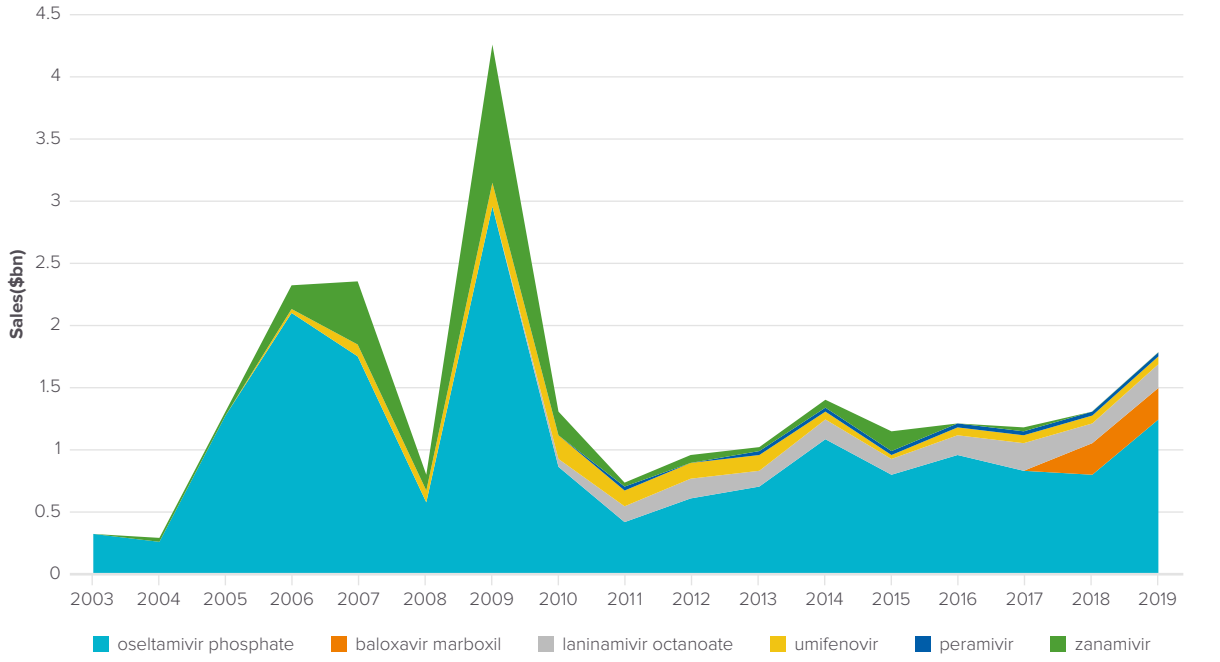
At time of writing no new trials had been announced, and Gilead's remdesivir remains the biggest near-term hope for a treatment, from any approach. The first reliable clinical data from trials run in China should start to emerge in the coming weeks, and even a relatively weak signal could still trigger substantial usage.

At this stage it is impossible to know how big a product remdesivir might become – Gilead has said it is committed to making it accessible, and talk of profit is a sensitive subject. The chart below shows that Roche certainly did well out of Tamiflu: to the end of 2019 the Swiss pharma giant had booked cumulative sales of $15.9bn, since launch in 1999.

Annual sales peaked at just over $1bn in 2014; and all these figures exclude sales booked by other companies that now make Tamiflu.

Antiviral sales

Source: EvaluatePharma® April 2020



Developers and manufacturers of antivirals in chart on previous page
Oseltamivir
Roche – sells as Tamiflu
Yichang HEC Changjiang – sells as **KeWei** (HECPG) in China
Chong Kun Dang – sells as **Tamiflu** in S. Korea
Generic suppliers include: Hanmi; Amneal; Lupin
Zanamivir
Glaxosmithkline – sells as **Relenza**
Baloxavir
Roche – sells as **Xofluza**
Shionogi – sells as **Xofluza**
Perimivir
Biocryst – sells as **Rapivab**
Shionogi – sells as **Rapivab**
laninamivir
Daiichi Sankyo – sells as **Inavir**
Umifenovir (Russia and China only)
OTCPharma – sells as **Arbidol** in Russia
CSPC Pharma Group – sells in China

To estimate how much it might cost to develop remdesivir, *EvaluatePharma Vision* provides an estimate of how much was spent getting existing flu antivirals to market.

According to *EvaluatePharma Vision's* R&D Costs module, these trials will probably cost Gilead around $150m to run. Estimates of the phase III studies being run in China are also included – the much lower figures reflect the fact that it is substantially cheaper to run studies in this region. A description of how these costs are calculated is below.

Governments around the world have pledged to spend whatever it takes to find a treatment for Covid-19, though much of the initial expense here will fall on Gilead.

Coronavirus costs – antiviral development

Source: EvaluatePharma Vision® April 2020

Details	Estimated cost of trial ($m)	NCT ID
US sponsored studies		
Moderate Covid-19 disease, remdesivir vs SOC (n=600)	92	NCT04292730
Severe Covid-19 disease, two remdesivir regimens (n=453)	61	NCT04292899
NIAID sponsored adaptive Covid-19 treatment trial (n=394)	88	NCT04280705
Chinese sponsored studies		
Severe Covid-19 respiratory disease (n=453)	31	NCT04257656
Mild/Moderate Covid-19 respiratory disease (n=308)	21	NCT04252664
Estimated total clinical costs of developing Tamiflu	300	-
Estimated total clinical costs of developing Relenza	393	-

Getting a vaccine to market is likely to be much more costly, if only because the failure rate of these projects is expected to be much higher. Cepi has come forward with an estimate of how much money it might take to cross the finish line: $2bn.

The not-for-profit foundation wants funds for an extensive research programme aiming to have at least three candidates submitted for approval in 2021. Commercial developers are typically reluctant to discuss development costs of individual products, so this call for funding is interesting as it puts a figure of sorts on what level of investment might be required.

Back in 2008, when avian H5N1 flu was the pandemic of the moment, Glaxosmithkline said it had spent $2bn developing a vaccine. Establishing manufacturing is likely to be a very big part of this cost estimate, something that the Cepi figures seem to support.

Cepi's call for funding

Source: CEPI. April 2020

Cost and timing	To support....
$100m immediately	Phase I trials of eight candidates
$375m by end of March, 2020	Manufacturing of clinical trial material for phase 2/3 trials for 4-6 candidates, and prep for those trials. Initial investments to expand global manufacturing capacity.
$400m by end of June, 2020	Run phase 2/3 trials for at least 2 candidates, trial prep for global studies, and production of clinical trial materials. Further investments in global manufacturing capacity.
$500m - $750m in 2021	Completion of clinical testing and regulatory filings for at least three candidates. Establish global manufacturing capacity at three geographically distributed locations for up to 3 candidates.

EvaluatePharma Vision estimates that $745m was spent on trials of the various candidates that entered the clinic for the avian and swine strains of the flu. This estimate only includes studies that were listed on clinicaltrials.gov, so the real number could be higher still.

The table below singles out some of the more costly products that actually made it to market; several other programmes were abandoned before reaching regulators. And not all are still available: Arepanrix has been withdrawn owing to lack of demand after governments cancelled large orders as the threat of swine flu receded.

These figures only concern costs specifically related to running the clinical studies.

Estimated cost of selected pandemic flu clinical programmes

Source: EvaluatePharma Vision® April 2020

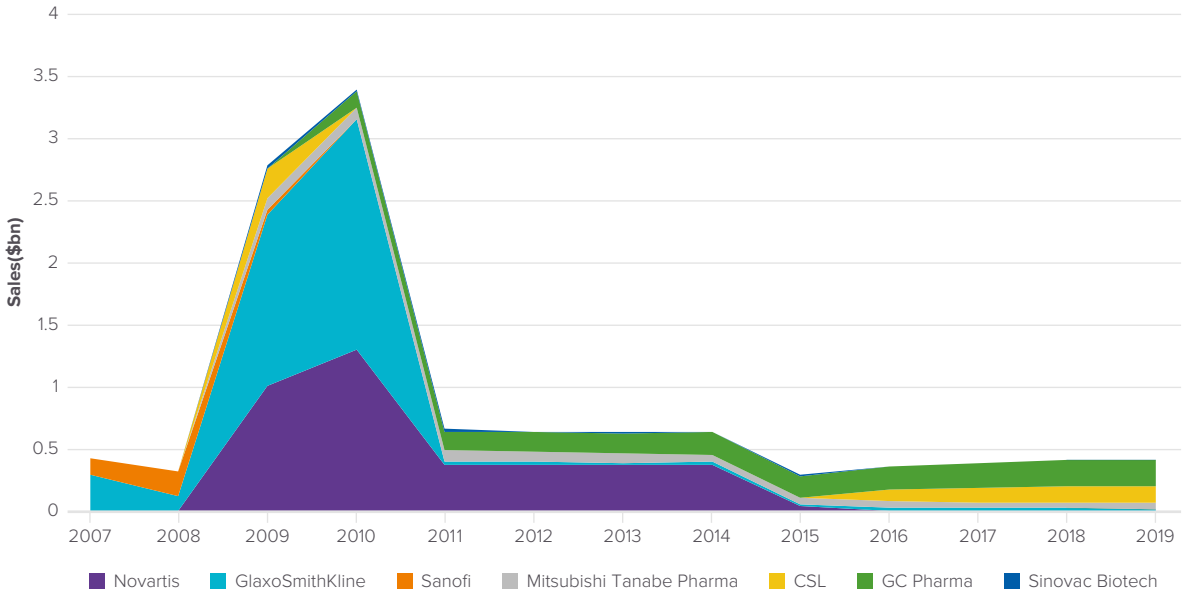
Product / Indication	Companies Involved	Total Trial Cost ($m) (Estimated)
Arepanrix; Swine (H1N1) influenza	Glaxosmithkline	95.1
Prepandrix; Avian (H5N1) influenza	GlaxoSmithKline	80.2
Vepacel; Avian (H5N1) influenza	Baxter (subsequently sold to Ology Bioservices)	70.8
Focetria; Swine (H1N1) influenza	Novartis (subsequently sold to CSL)	68.2
Audenz; Avian (H5N1) influenza	Novartis (subsequently sold to CSL)	60.2
Total cost of H1N1/H5N1 pandemic flu programmes		**745**

Still, vaccine makers managed to respond pretty quickly to previous deadly viral outbreaks: Glaxosmithkline, for example, put its first H5N1 candidate into the clinic in early 2006, and this became available a little over 12 months later.

And certain makers of swine and avian flu vaccines are still booking sales of these preventative shots, *EvaluatePharma* data show. South Korea's GC Pharma is a major supplier in Asia, while CSL is a big global player; the Australian company bought Novartis's flu vaccines business back in 2014. Government stockpiles will be the major customers here.

Sales from H1N1/H5N1 vaccines

Source: EvaluatePharma® April 2020

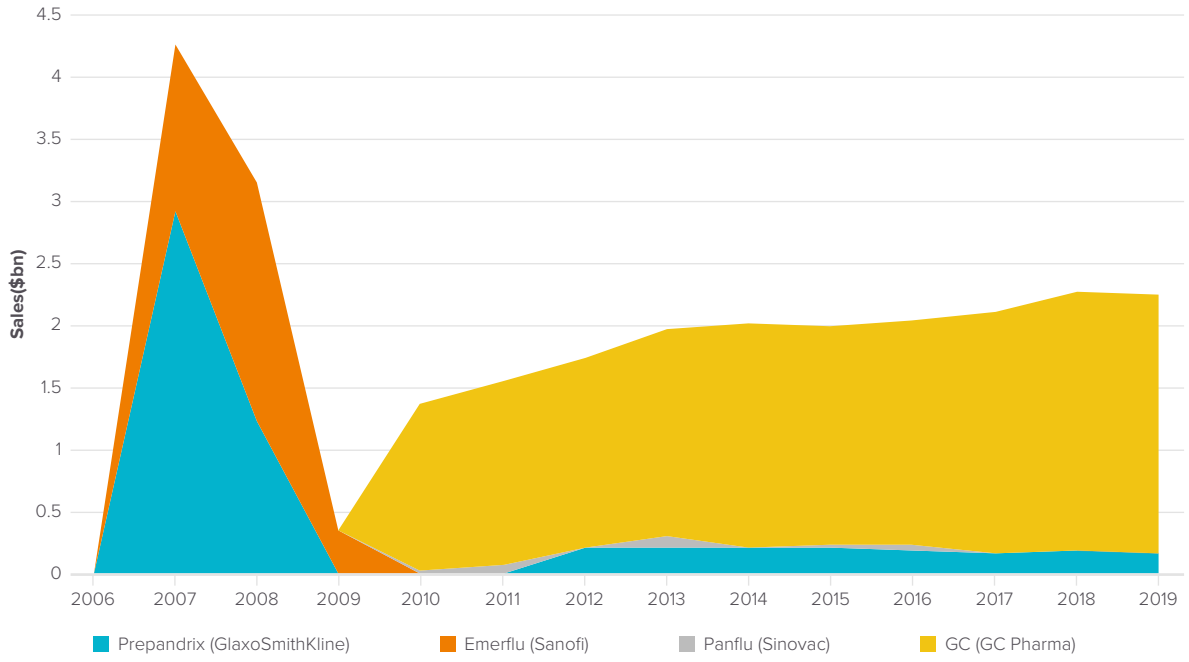


The coronavirus is a different proposition, of course, and it is not yet known what technology might produce the first vaccine against Covid-19. Among the big beasts Sanofi and Johnson & Johnson both have research under way, while Moderna and Biontech are applying their respective RNA platforms to the problem.

Still, lessons learned during the swine flu outbreak a decade ago show why these big manufacturers might be cautious about the opportunity: both Glaxo and Baxter had substantial contracts cancelled as the threat of the virus abated. Given the trajectory of Covid-19 and the global disruption it is causing, it seems likely that any future vaccine could become part of stockpiles, and turn into products that look like those below.

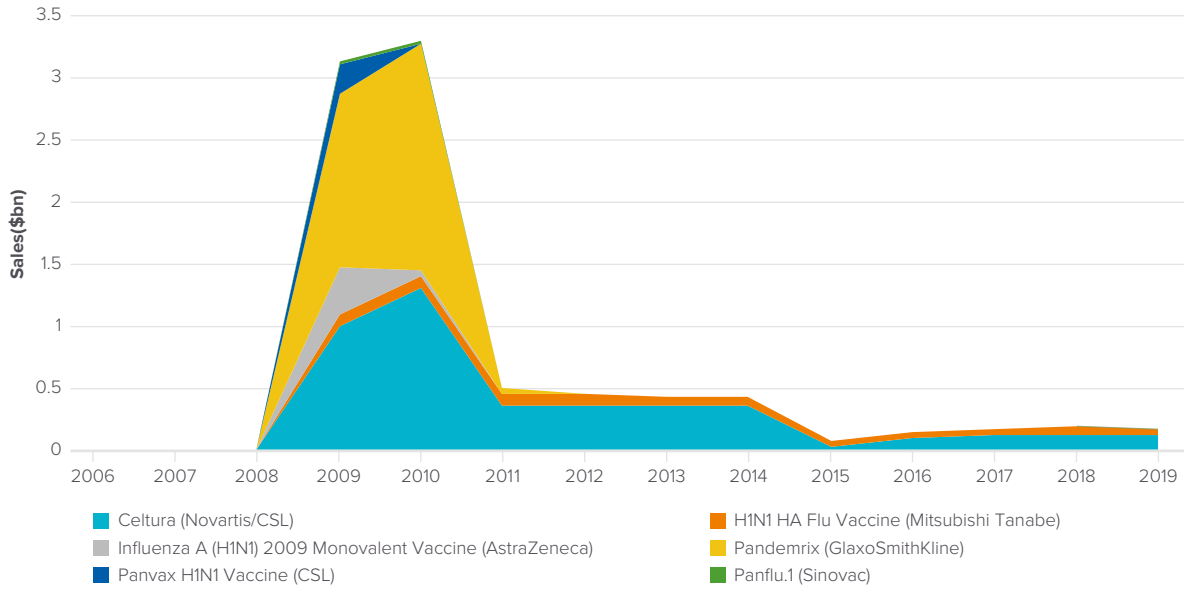
H5N1 vaccine sales

Source: EvaluatePharma® April 2020



H1N1 vaccine sales

Source: EvaluatePharma® April 2020



Much of the world's traditional vaccine manufacturing capacity lies with a fairly small number of companies – in the west, at least – and it is to these groups that the World Health Organization would likely turn should a preventative treatment for Covid-19 be found.

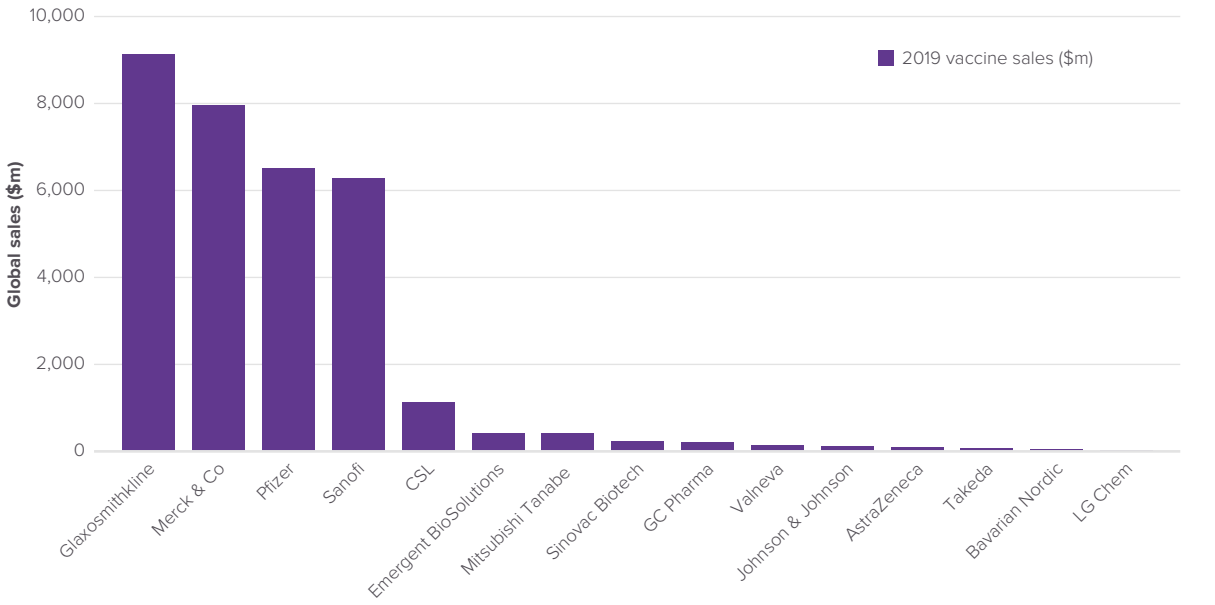
Years of asset swapping and consolidation has focused this capability into the hands of four global majors, although two of these rely on dominant products: Pfizer derives 90% of its vaccine sales from the pneumococcal jab Prevnar 13, while almost half of Merck & Co's business is in Gardasil, against HPV infection, *EvaluatePharma* data show.

A Covid-19 vaccine based on RNA technology from the labs of a specialist developer could well be the first to emerge. However, when it comes to manufacturing, scale will be required.

To deliver and distribute at global volumes, it seems pretty likely that some of these big players listed below would become involved.

The world's biggest vaccine makers

Source: EvaluatePharma® April 2020



Global vaccine companies and their specialisms

Source: EvaluatePharma Vision® April 2020

Company	Area of specialism	2019 vaccine sales ($m)
Glaxosmithkline	Broad, incl, flu, childhood and shingles vaccines	9,139
Merck & Co	Broad, incl, childhood and HPV vaccines	7,967
Pfizer	Primarily a pneumococcal focus, also some childhood and travel vaccines	6,504
Sanofi	Broad, incl. flu, childhood and travel vaccines	6,293
CSL	Seasonal and pandemic flu	1,124
Emergent BioSolutions	Anthrax, smallpox, other bioterrorism threats	415
Mitsubishi Tanabe	Broad, incl. flu, childhood and travel vaccines (Japan)	414
Sinovac Biotech	Broad, incl. flu and childhood vaccines (China)	244
GC Pharma	Broad, incl. flu and childhood vaccines (S. Korea)	208
Valneva	Japanese encephalitis and cholera	141
Johnson & Johnson	Broad, incl. childhood and travel vaccines	118
AstraZeneca	Nasal spray delivered flu vaccine	106
Takeda	Mainly childhood vaccines (Japan)	73
Bavarian Nordic	Small pox	49
LG Chem	Broad, incl. flu, childhood and travel vaccines (Asia)	28

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