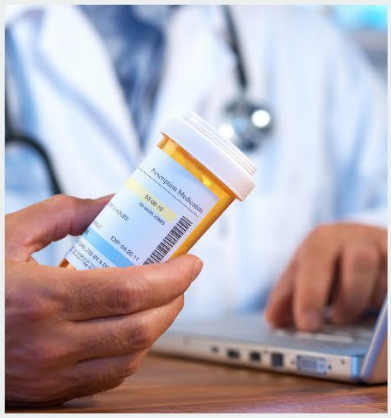
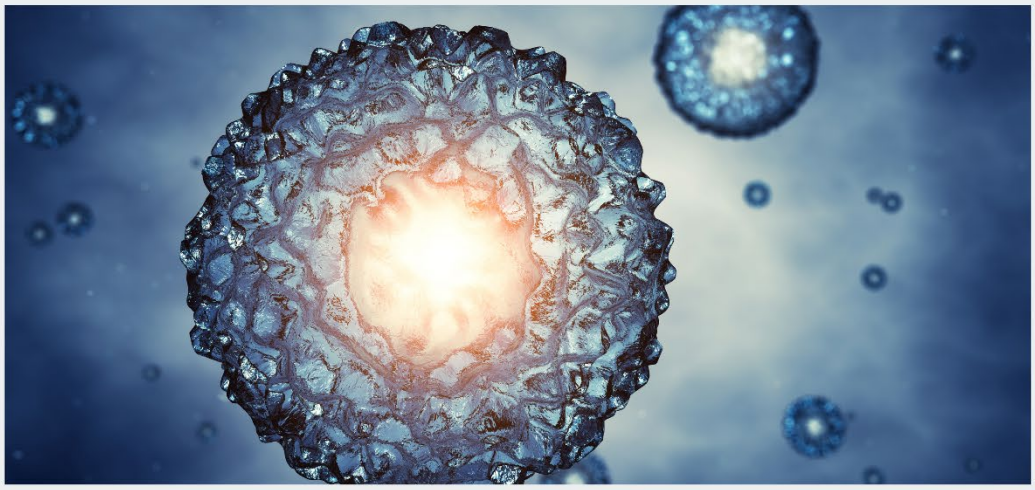
BIOPHARMA

Biopharma in the COVID-19 World

Reflecting on Past Challenges and Evaluating Emerging Trends





HEALTH ADVANCES

Strategy Consultants for the Healthcare Industry

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Introduction

COVID-19 has proven to be a devastating and unprecedented global health crisis. The pandemic is especially complex for biopharma. The industry has been called upon to rapidly find therapeutics and vaccines that can treat, cure, or prevent the disease. Regulators are facilitating frenzied development efforts with new emergency approval programs. But, the only novel treatment to have emerged thus far – Gilead's remdesivir – has been criticized for its cost, as was Moderna's announcement on the target price for its frontrunner Covid-19 vaccine . Meanwhile, the precipitous economic downturn is affecting topline revenues and access to capital; clinical development timelines are under pressure as COVID-19 has limited access to trial sites; and supply chains are coming under scrutiny as governments seek to ensure reliable access to treatments.

In this eBook, we explore some of the key challenges highlighted above. We consider how the biopharma industry has been impacted by crises and recessions in the past, and how it is currently endeavoring to develop treatments for COVID-19, including more near-term antibody treatments and longer-term vaccines.

- Our biopharmaceutical sales resilience chapter looks back at how biopharma fared during the great recession of 2008-2009 and draws lessons for today's biopharma companies who are facing similarly perilous economic conditions.
- In our protective antibody chapter, we discuss the prospects for plasma-derived and recombinant antibodies to serve as a treatment (perhaps even prophylactically) for COVID-19 patients. These treatments may be a bridge to an effective vaccine, but have unique challenges related to supply, quality, treatment protocols, and regulatory guidance.
- In our final chapter, we discuss the outlook for the ultimate solution: a vaccine. Here, we review some of the more novel approaches which have greatly accelerated development timelines (e.g., Moderna's mRNA vaccine) and compare them to slower but perhaps more reliable methods (e.g., Janssen's adenoviral vaccine candidate).

At Health Advances, we're exploring these and other ways in which COVID-19 may change the global healthcare industry in an ongoing blog series. Health Advances has always been at the forefront of technological innovations and industry trends in methods and models for providing healthcare. We help our clients understand the future, so they can make more informed strategic decisions today.

Biopharma Sales Resilience through Economic Recession

Analysis of 2008/9's Great Recession on the Sales of Established, Branded Drug Classes
May 2020

Executive Summary

- The biopharma industry is generally more resilient to recessions than the overall healthcare sector, as witnessed through industry sales and biotech market capitalizations
- That said, biopharma sales do face pressures from a recession's economic fallout, as uninsured and Medicaid populations rise, and as private payers more aggressively manage drug spend
- We hypothesized that a given drug class' resilience to a recession would be driven by four key criteria: indication severity, indication acuity, drug effectiveness, and the level of competition
  - These criteria would impact the degree to which patients defer drug treatment and payers restrict or manage access to the class
  - Our resilience index correlates well with sales growth pre vs. post-recession, based on our analysis of sales of 13 branded drug classes during the 2008/9 Great Recession
- Based on our biopharma sales resilience analysis:
  - Branded drug classes that are highly effective, treat severe and/or acute indications, and face few competitors or alternatives are most resilient to recessions
  - For those drug classes that address less severe indications or face low-cost alternatives, drug manufacturers need to work to ensure continued access and adherence. We provide several recommendations and examples

Recession Effects on the Biopharma Industry

The biopharma industry is generally more resilient to economic recessions than other sectors, including the broader healthcare sector.

In 2009, while the global economy contracted at -2%, pharma sales continued to grow at 2% (Figure 1). While this growth figure was substantially lower than prior years, it was markedly better than the overall economy.

Moreover, biopharma share prices outperformed the broader healthcare sector. The NASDAQ biotech index retuned to pre-recession levels faster than the Dow Jones US Healthcare index and the S&P 500 economy (Figure 2). In December 2009, the NASDAQ biotech index reached its pre-recession (i.e., December 2007) levels. It took until April 2011 for the Dow Jones US Health index to recover to these levels and the S&P500 didn't recover until February 2013.

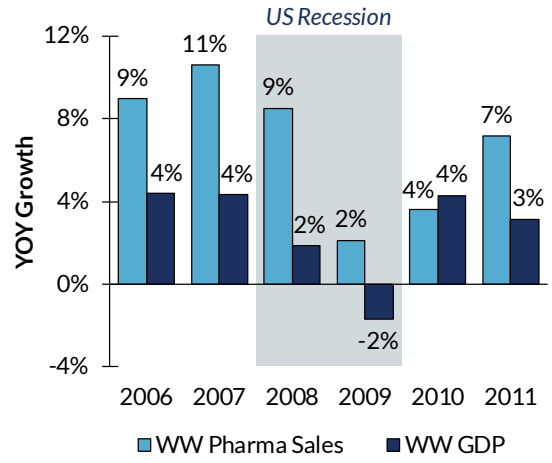


Figure 1: WW Pharmaceutical Sales Growth versus Worldwide GDP

Source: Health Advances analysis, EvaluatePharma, Thomson Eikon.

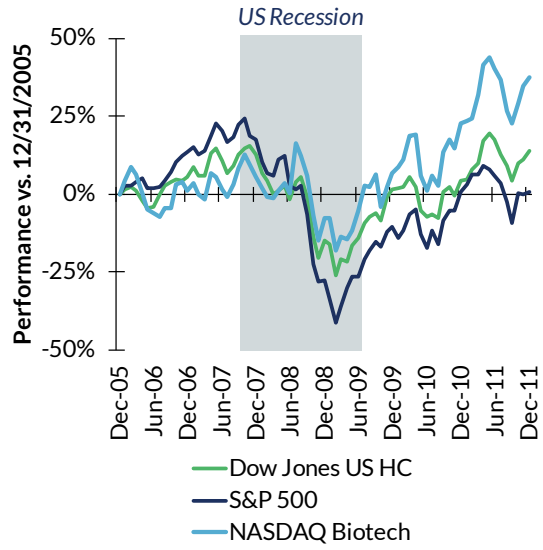


Figure 2: Share Price Performance for Various Indices (2005-2011)

Source: Health Advances analysis, Thomson Eikon.

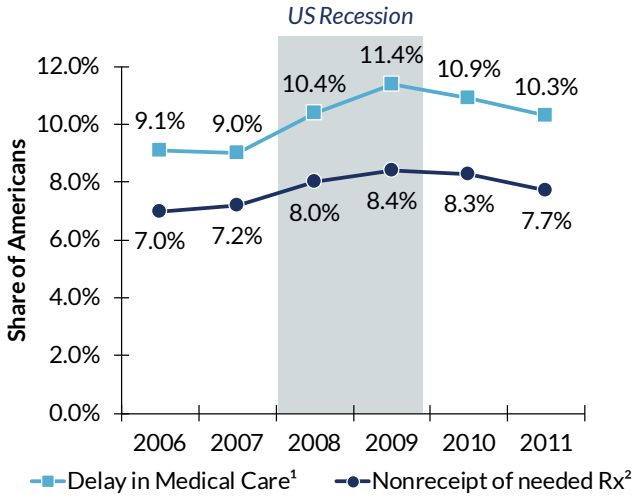


Figure 3: Deferral Rates of Medical Services and Prescriptions

[1] *Based on persons responding to the questions, "During the past 12 months was there any time when person needed medical care but did not get it because person couldn't afford it?" and "During the past 12 months has medical care been delayed because of worry about the cost?"*

[2] *Based on persons responding to the question, "During the past 12 months was there any time when person needed prescription medicine but didn't get it because person couldn't afford it?*

Source: Health Advances analysis, CDC NCHS.

Partly explaining biopharma's resilience, consumer surveys indicate that patients are less likely to defer prescriptions than medical services. In 2009, 11.4% of Americans deferred medical services, while prescriptions were deferred at a rate of only 8.4% (Figure 3). Patients may defer services and procedures more readily because those tend to be more time-consuming and disruptive than filling a prescription. Also, some prescriptions have lower out-of-pocket costs than office visits and procedures.

However, Biopharma does face some fallout from recessions, driven by larger uninsured and Medicaid populations and more aggressive access restrictions by payers.

In the US, biopharma experiences two key negative impacts that constrict growth during recessions: (1) uninsured populations and Medicaid populations increase, and (2) commercial payers manage access to therapeutics more aggressively (figure 4).

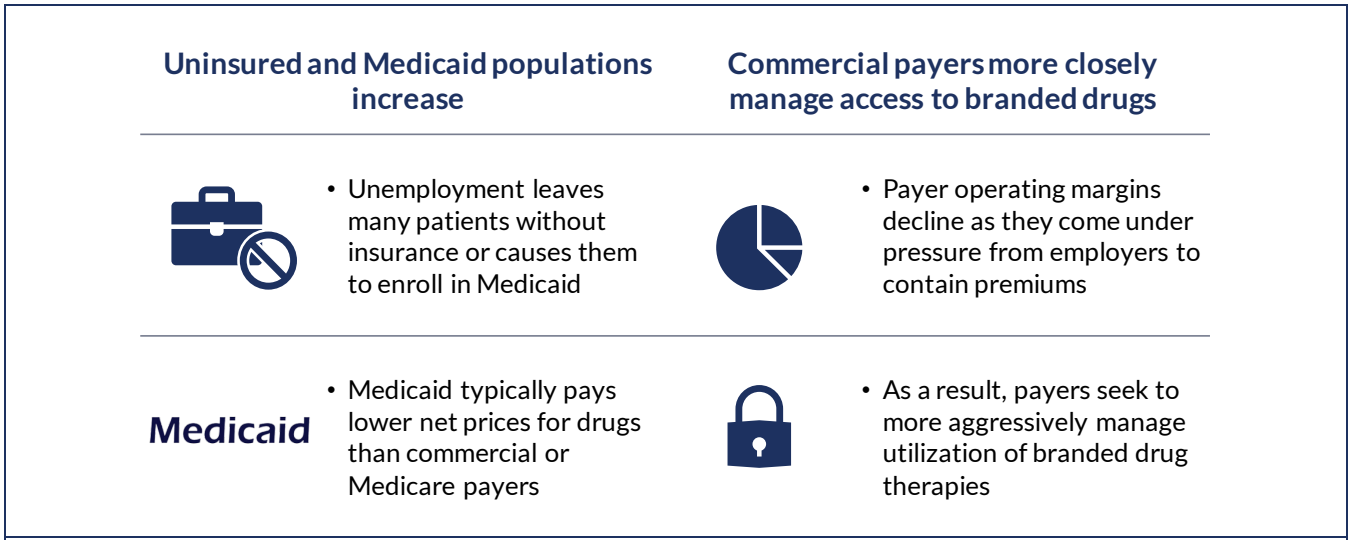


Figure 4: Recession Factors Impacting Biopharma

Source: Health Advances.

Medicaid enrollment increased from ~43MM before the recession to ~52MM after the recession. Unsurprisingly, this increase tracked with the spike in unemployment that accompanied the recession (Figure 5). While Medicaid ensures that patients continue to have medical coverage and receive treatment, it pays substantially lower rates than other US payers, including Medicare (Figure 6). An analysis by the congressional budget office showed that Medicaid prices for specialty medications were on average ~49% less than Medicare. Medicaid prices for non-specialty medications were ~72% less[1].

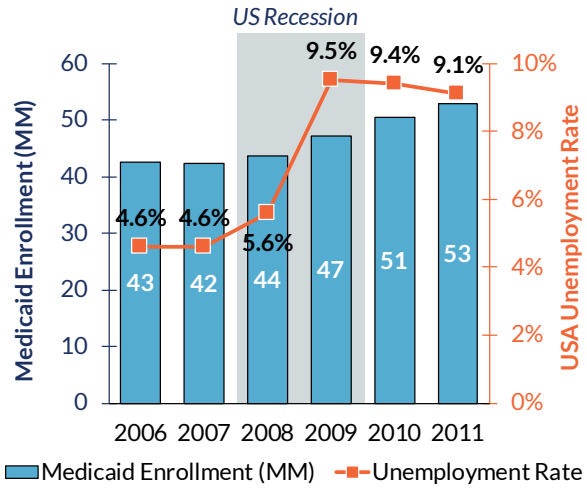


Figure 5: Medicaid and Medicare net prices for specialty and non-specialty prescriptions.
Source: Health Advances analysis, Congressional Budget Office.

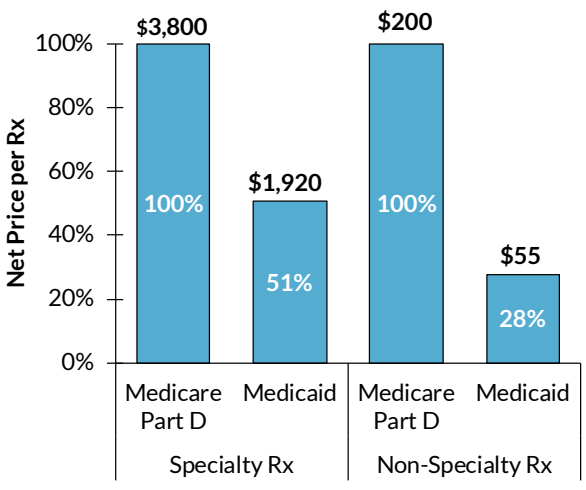


Figure 6: Payer operating margins. Weighted average of Aetna, UnitedHealthcare, Cigna, Humana
Source: Health Advances analysis, SEC filings.

Operating margins of large payer organizations declined in the 2008 recession, leading to more aggressive control of drug utilization and spend.

Commercial payers come under substantial stress during recessions. Operating margins for major US commercial payers declined from a high of ~8.6% in 2007 to a low of ~6.1% in 2009 (Figure 7). As a result, payers seek to tighten access to drugs.

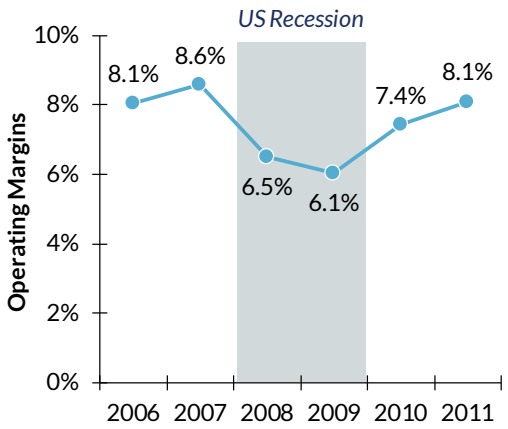


Figure 7: Distribution of covered lives by number of co-pay tiers. HMO plans only. 2006 data not available.
Source: Health Advances analysis, Sanofi Aventis Managed Care Digest.

Payers used several strategies to control drug costs.

- ***Multi-tier plans*** enable payers to steer patients to lower-cost alternatives by creating additional co-payment tiers. The more tiers a payer has available, the more finely they can tune incentives across the formulary. Among HMO plans, 4- or 5-tier plans grew from 6.2% of covered lives to 16.1% of covered lives between 2005-2011 (Figure 8).

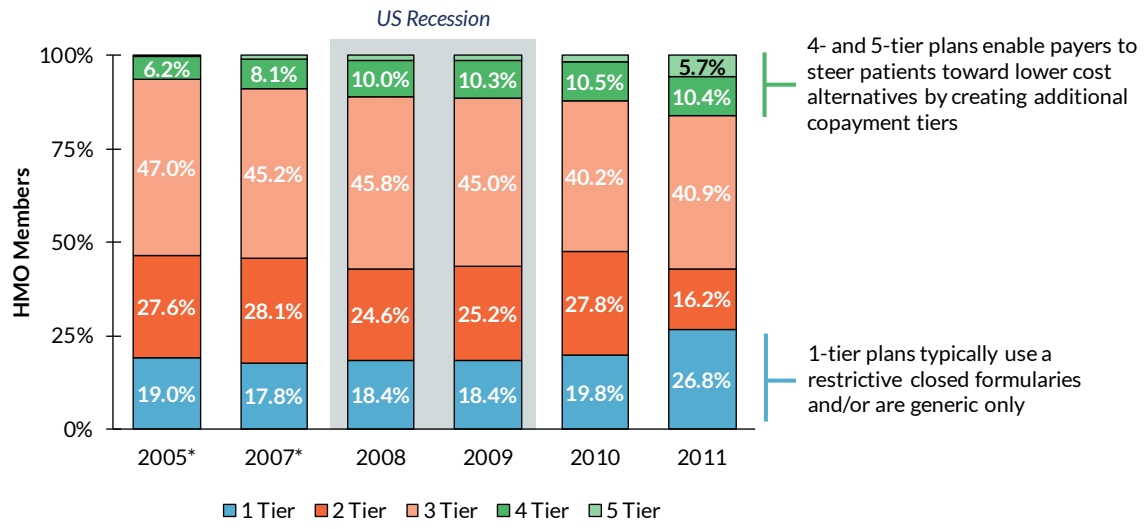


Figure 8: Distribution of Covered Lives by Number of Co-Pay Tiers (HMO Plans Only. 2006 Data not Available)
Source: Health Advances analysis, Sanofi Aventis Managed Care Digest.

- ***Closed formularies*** allow payers to limit members to a subset of therapies. Drugs not on the formulary are not covered or only covered after a prior authorization process. For example, some closed formularies limit members to a single drug within a class. Some estimates suggest HMOs save 10% to 25% of their drug expenditures through closed formularies. The recession accelerated a trend towards closed formularies: Closed formularies grew from 38% to 50% of

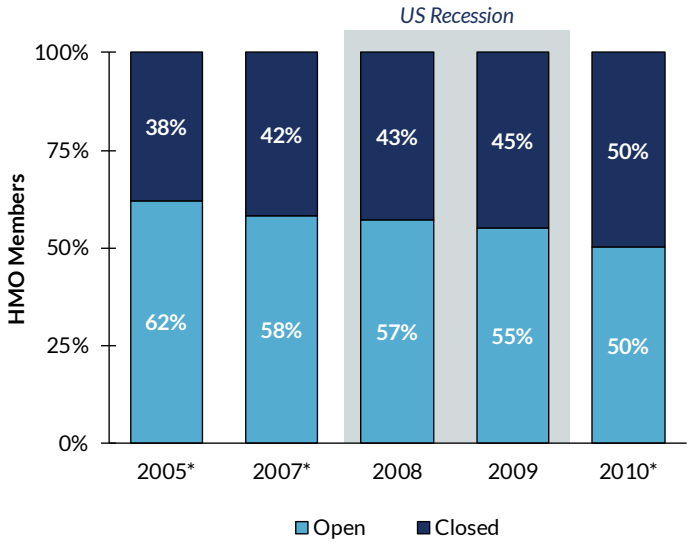


Figure 9: Distribution of Covered Lives by Open vs. Closed Formularies (HMO plans only. 2006 and 2011 data not available)
Source: Health Advances analysis, Sanofi Aventis Managed Care Digest.

We hypothesized that in an environment of stricter payer access and higher uninsured and Medicaid populations, sales of drugs that uniquely and effectively treat severe and/or acute diseases are more resilient. (Figure 10)

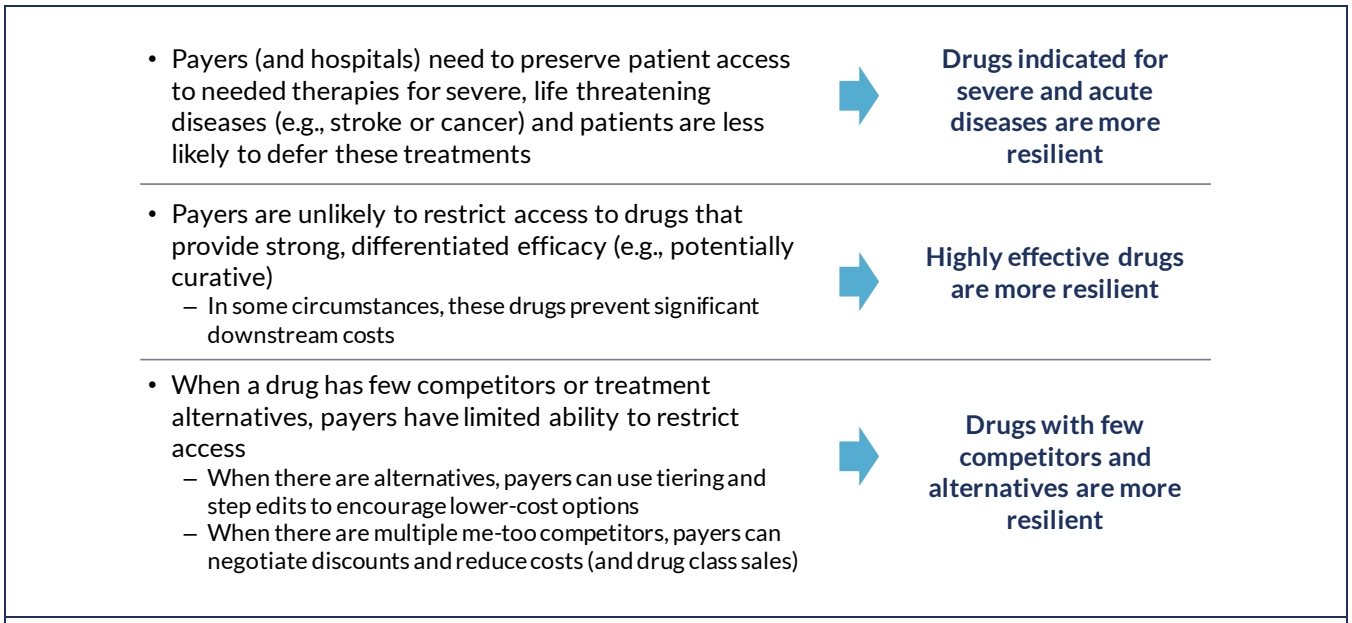


Figure 10: Hypotheses on Drug Sales Resilience
Source: Health Advances analysis.

Sales Resilience of Specific Branded Drug Markets

We assessed a drug class' resilience index according to four criteria: severity, acuity, efficacy, and competition.

In order to evaluate our hypothesis, we developed a means of rapidly scoring different drug classes, which we called the ***resilience index*** (Figure 11). This index considers four key market and competitive criteria (described below), each of which was scored from 1 (low) to 3 (high). We hypothesized that where the resilience index is high, the sales growth of the class would be better preserved during a recession.

- ***Indication severity*** is the magnitude of impact that an indication has on a patient's life. It ranges from quality of life impact to significant mortality impact.
- ***Indication acuity*** is the time period over which an indication manifest. Acute indications have sudden onset and often require immediate treatment (e.g., heart attack). Chronic indications are long-developing syndromes (e.g., asthma).
- ***Drug efficacy*** is the magnitude of benefit provided by the medication class. It ranges from treatments that only address symptoms and do little to affect the underlying disease course to potentially curative treatments.
- ***Drug Competition*** is the availability of either in-class competitors or out-of-class alternatives.

	Resilience Index: Low → High			Examples	
	1	2	3	EGFR TKIs	Parathyroid Hormone
Indication Severity	Quality of life	Morbidity impact; no or little mortality impact	Mortality Impact	3	2
Indication Acuity	Chronic		Acute	2	1
Drug Efficacy	Symptomatic Treatment	Disease-modifying	Potentially Curative	2	2
Drug Competition	>2 Competitors in the same class OR highly attractive low-cost alternatives	1-2 competitors in the same class OR moderately attractive low-cost alternatives	Only drug in the class AND no low-cost alternatives	3	2
			Scaling Factor	-4	-4
			Resilience Index	**6**	**3**

Figure 11: Health Advances Resilience Index
Note: EGFR TKIs = epidermal growth factor receptor tyrosine kinase inhibitors
Source: Health Advances.

In order to evaluate the sales performance of a drug class, we created a growth score, which compared the change in compound annual growth from 2006-2008 to 2009-2011 (effectively, before and after the recession). If the difference was significantly positive, growth accelerated following the recession. If it was significantly negative, growth decelerated after the recession. A difference near zero indicated the growth was unaffected by the recession (Figure 12).

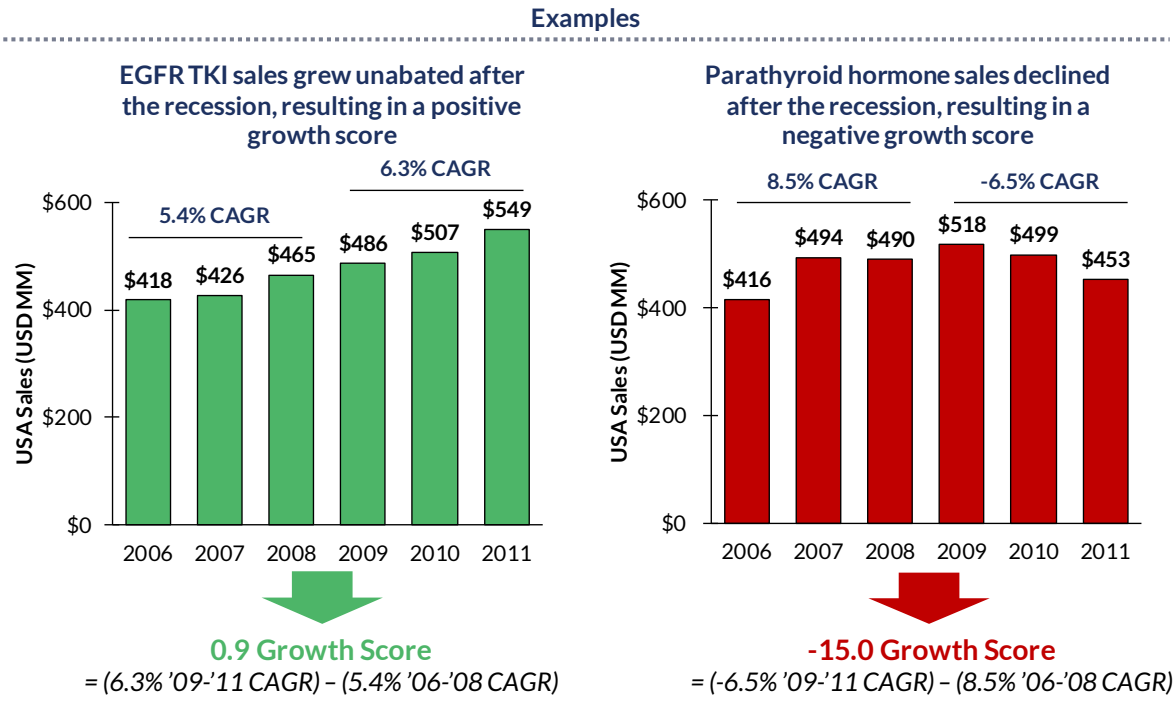


Figure 12: Example Growth Score Calculations used to Evaluate Drug Class Sales Performance before and after the 2008-2009 Recession

Source: Health Advances analysis, EvaluatePharma.

Our analysis of biopharma sales through the 2008/9 Great Recession shows that drug classes with high resilience treated severe conditions, offered strong efficacy, and faced limited competition.

When we analyzed our growth scores against our resilience index, we saw a high resilience index is strongly correlated with a high growth score (figure 13).

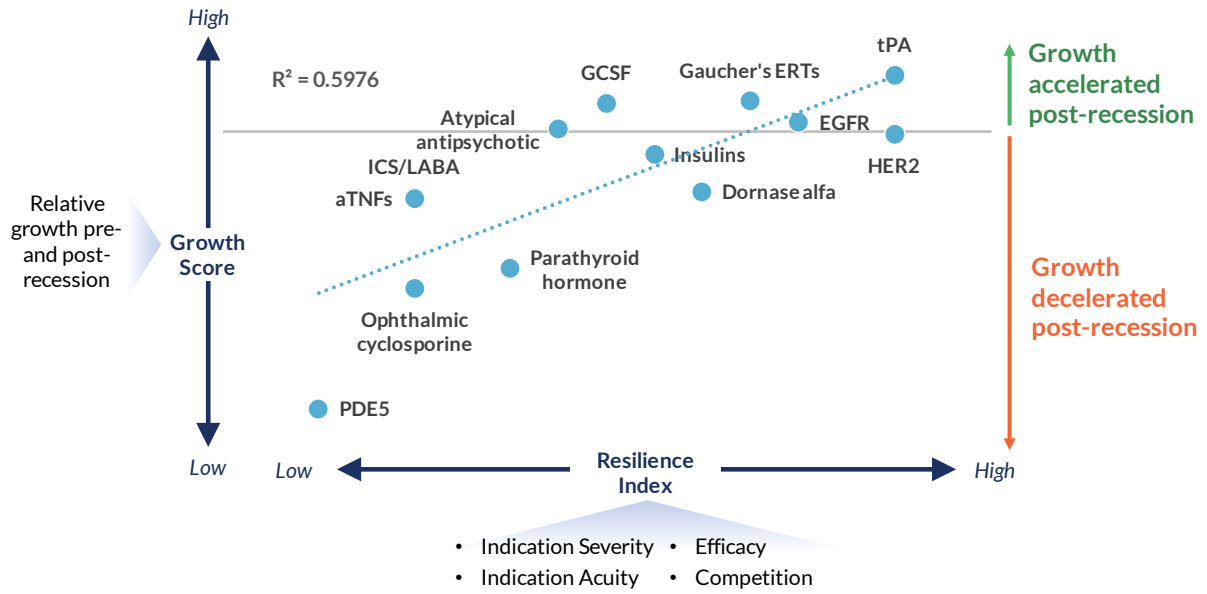


Figure 13: Biopharma sales Resilience (Growth Score vs. Resilience Index for N=13 Branded Drug Classes)

Note: GCSF = Granulocyte-colony stimulating factor. ICS/LABA = combination inhaled corticosteroid and a long-acting beta-agonist. ERT = Enzyme replacement therapy. tPA = Tissue plasminogen activator. EGFR = Epidermal growth factor receptor. HER2 = epidermal growth factor receptor 2. aTNF = Anti-Tumor necrosis factor. PDE5 = phosphodiesterase type 5.

Source: Health Advances analysis, EvaluatePharma.

The analysis revealed two broad sets outcomes (figure 14):

- Markets with a high resilience index experienced limited impact to their sales (i.e., sales neither accelerated nor decelerated).
- Markets with a low resilience index experienced a significant downturn in their sales performance.

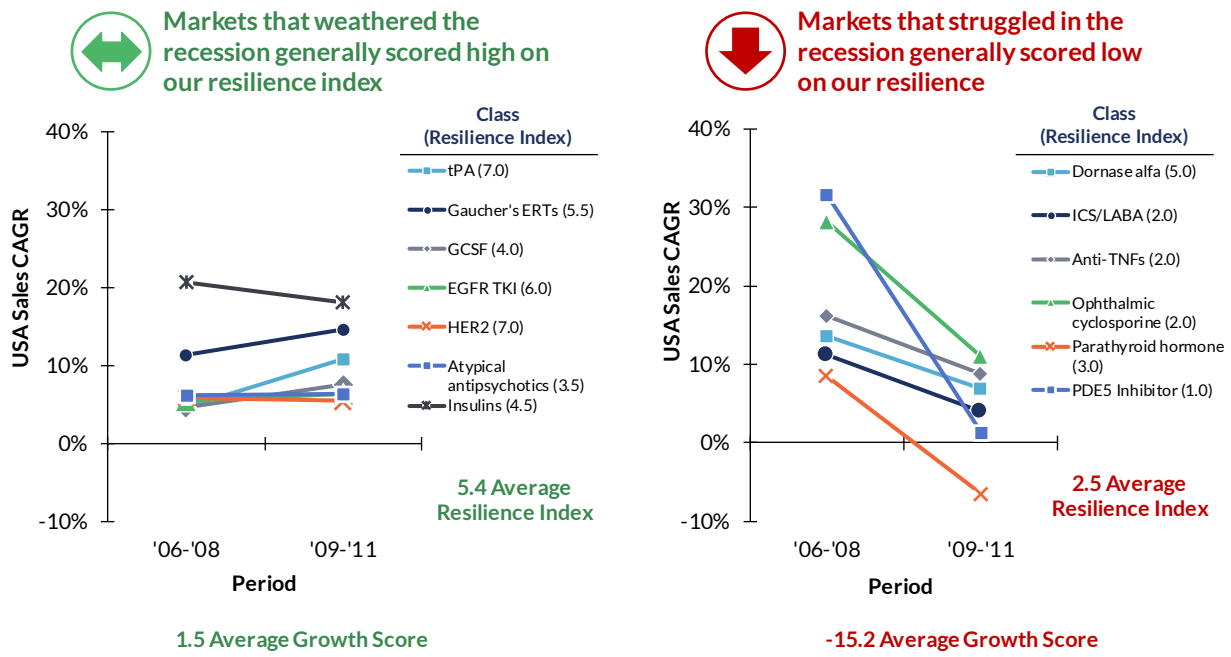


Figure 14: Sales Performance for Markets with High and Low Resilience Indices

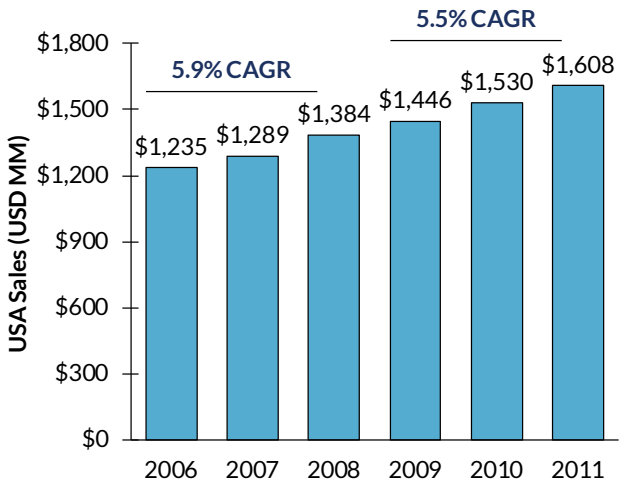
Note: tPA = tissue plasminogen activator. ERT = enzyme replacement therapy. GCSF = granulocyte colony-stimulating factor. EGFR TKI = Epidermal growth factor receptor tyrosine kinase inhibitor. EPO = erythropoietin. HER2 = human epidermal growth factor receptor 2. TNF = Tumor necrosis factor. PDE5 = phosphodiesterase type 5.

Source: Health Advances analysis, EvaluatePharma.

Case Studies

CASE STUDY 1

Herceptin, the only targeted HER-2 antibody, grew steadily through the recession given the severity of the cancer indication and lack of comparably effective alternatives.

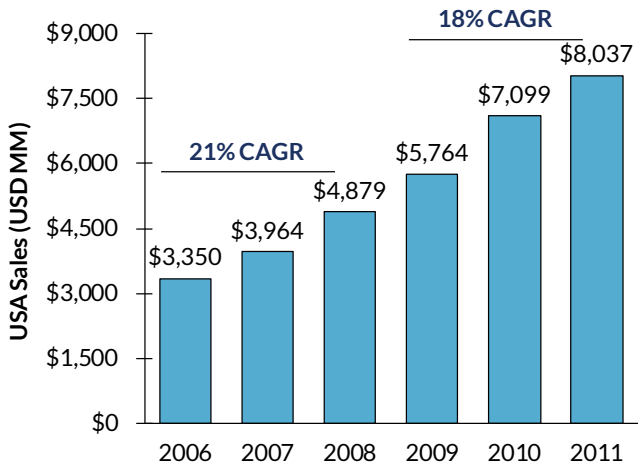


- Herceptin was the first targeted therapy for HER-2 positive breast cancer. It dramatically improved the treatment of this disease
  - Herceptin is indicated for metastatic breast cancer or as an adjuvant treatment for breast cancer
  - One out of five breast cancer cases is HER-2 positive, and this type tends to be more aggressive
  - In combination with surgical resection, treatment with Herceptin may be curative
- Herceptin's annual growth rate pre and post-recession remained stable at 5-6%

Source: Health Advances analysis, EvaluatePharma, Wang 2019 Signal Transduct Target Ther, Nan Jiang 2018 Exp Ther Med, Romond 2005 NEJM.

CASE STUDY 2

An essential therapy for many, insulin sales growth continued unabated through the recession

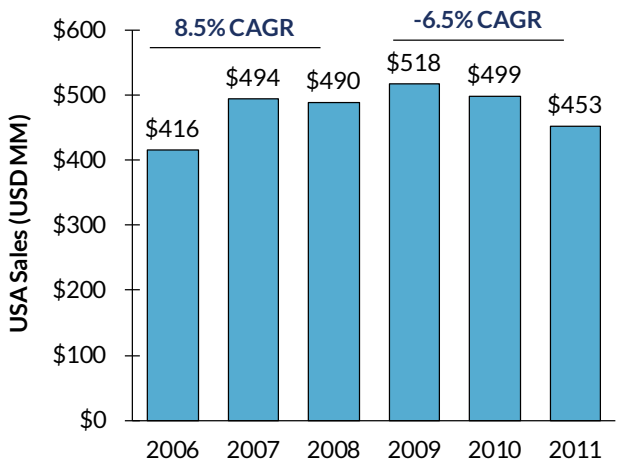


- Many diabetes patients require chronic insulin to manage their disease
  - For people with type 1 diabetes, there is no substitute for insulin therapy
  - People with type 2 diabetes may manage their diseases with oral medications and diet and exercise, but many progress to insulin dependence
- Insulin sales continued to grow rapidly through the recession (~20% CAGR), driven by:
  - Strong adoption of newer analog insulin therapies – Lantus, Novolog and Humalog
  - Patient access supported by payers despite net price increases

Source: Health Advances analysis, EvaluatePharma, UpToDate, DeWitt JAMA 2003.

CASE STUDY 3

Parathyroid hormone sales declined post recession as patients increasingly relied on generic bisphosphonates

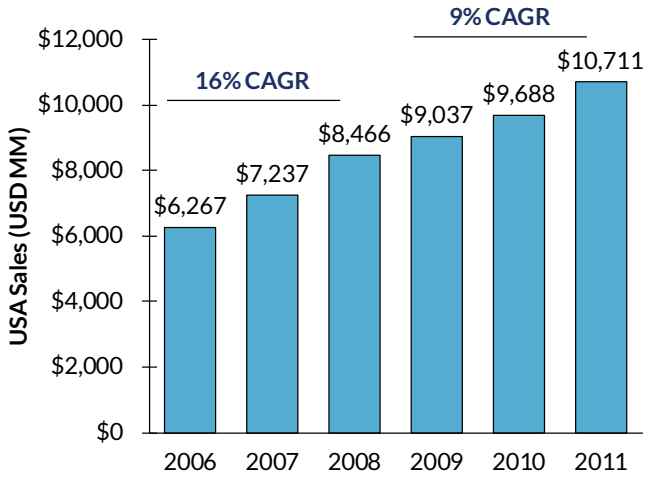


- Forteo is a form of parathyroid hormone used to treat osteoporosis
  - Before 2017, it was the only treatment that catalyzed new bone creation, rather than slowing degradation
  - Forteo is typically reserved for patients more severely affected by osteoporosis
- Forteo sales dropped post recession, as patients remained on generic bisphosphonate therapy
  - In 2008, the patent for a leading bisphosphonate, Fosamax, expired
- While Forteo is more effective than bisphosphonates, osteoporosis patients don't typically experience acute symptoms and may have chosen to remain on a cheap generic

Source: Health Advances analysis, EvaluatePharma, Mayo Clinic, Smith 2008 CNN Money.

CASE STUDY 4

Anti-TNFs sales growth slowed post recession as patients deferred biologic treatment



- Anti-TNFs are premium-priced biologic therapies to treat moderate-severe chronic inflammatory conditions, including rheumatoid arthritis (RA), Crohn's disease, and psoriasis
  - Anti-TNFs are typically prescribed in combination with generic methotrexate or other oral options
- Payer restrictions and patient discontinuations slowed sales growth during the recession
  - Increased co-pays and loss of insurance led to an increased number of discontinued/deferred treatments
  - Payers enacted strict step edits and prior authorization requirements resulting in a reduced number of new patients starting on anti-TNF therapy

Source: Health Advances analysis, EvaluatePharma, Mangoni 2019 BMC Rheumatol, Fortune, AbbVie 10-K, Abbot equity analyst reports.

Implications for Industry

Our analysis reveals the added importance of market access and adherence for drug manufacturers during economic recessions.

- Our resilience index can be used as a heuristic to assess a brand or branded class' sales risk during a recession
  - Generally, indication severity, indication acuity, drug effectiveness, and the level of competition can help gauge a recession's level of impact on sales growth
  - Health Advances can also help with more targeted market evaluations to develop tailored assessments of sales risk and to develop strategies to mitigate risk.
- For drug classes that are less resilient, drug manufacturers need to facilitate drug access and adherence for their patients. This may be achieved by:
  - Enabling faster and simpler enrollment (and re-enrollment) into patient support programs as well as relaxing criteria for enrollment (e.g., immediate access for patients recently unemployed)
  - Enhancing programs to reduce patient costs, including providing temporary free therapy for unemployed patients to ensure continuity of care and reducing barriers to using these benefits
  - Developing solutions to assist patients with prescription fulfillment and adherence
  - Working with payers to alleviate prior authorizations and other utilization management tools, leveraging real-world and health economic evidence

Several large pharma companies recently bolstered their patient support programs to ensure continuity of care for their patients and limit the impact of COVID-19 (Figure 15).

MERCK

- Adapted the Merck Patient Assistance Program for patients who lost their job or cannot see their doctor
  - Assessing patients' real-time financial situations
  - Providing assistance with expiring enrollments
  - Offering new options to collect signatures on enrollment forms
- Expanded other access and assistance programs
  - Temporary $0 co-pay for some products for eligible privately insured patients
  - Relaxed some refill restrictions related to coupon use

Bristol Myers Squibb™

- Expanded its patient support programs to help eligible unemployed patients affected by COVID-19
- Expanded program offers free medicine and features include:
  - Immediate access for patients who have lost their employment and health insurance
  - A simple, single point of entry
  - Streamlined enrollment process
  - Vouchers to assist with continuity of care for several self-administered BMS medicines, for eligible patients

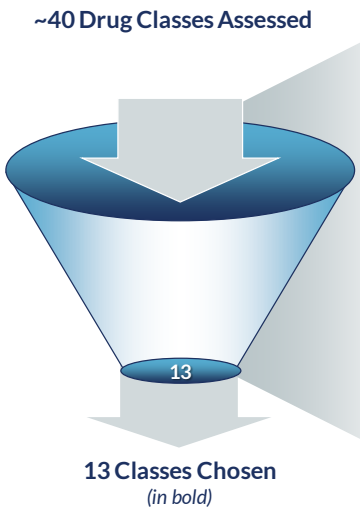
NOVARTIS

- Enhanced offerings to help patients experiencing difficulties from the COVID-19
  - Simplified access to free medicines for eligible patients
  - Expanded programs to improve affordability and patient support
    - Free temporary supplies of certain medications to avoid treatment gaps
    - Expanded in-home onboarding and administration support
    - Extended fill co-pay card support
    - Where available, extended refills for free-drug programs

Figure 15: COVID-19 Industry Examples (Publicly Announced)
Source: Health Advances analysis, company website and press releases.

Notes on Methodology

Health Advances rapidly evaluated ~40 drug classes to select 13 classes that could best reflect recession impact – e.g. established class, all branded (no generic options) (Figure 16).



- 5-HT3 antagonists
- Acetylcholinesterase inhibitors
- **Alteplase/tPA**
- Alpha Blockers
- Aminoketone antidepressants
- Amphetamines
- Antimigraine triptans
- **Anti-TNFs**
- **Atypical Antipsychotics**
- Contraceptive Implants
- DPP-4 inhibitors
- **EGFR**
- EPO
- **Gaucher's ERTs**
- **GCSF**
- **HER2**
- HIV combo therapies
- **ICS/LABA**
- **Insulins**
- Isotretinoin for Acne
- Nasal Corticosteroids
- Non-Barbiturate Hypnotics
- **Parathyroid hormone**
- **PDE5s**
- Clopidogrel
- PPIs
- Pregabalin
- Prostaglandin analogs
- **Dornase alfa**
- **Ophthalmic cyclosporine**
- SNRI
- Statins

Classes were excluded primarily due to generic entry or because they were early in their growth trajectory

Figure 16: Method of Selecting Drug Classes for Analysis
Source: Health Advances analysis.

Details on Evaluated Drug Classes

Market/ Drug Class	Example Therapeutic	First Drug Launch/ LOE	Resilience Score	CAGR '06-'08	CAGR '09-'11	Description
HER2 Therapies	Herceptin	1998 / 2019	7	6%	5%	• Effective and highly targeted treatment for metastatic breast cancer patients • Potentially curative in a potentially fatal disease
Tissue Plasminogen Activator	Activase	1987 / 2025[2]	7	5%	11%	• Effective treatment for acute ischemic stroke • High mortality impact, critically acute treatment
EGFRs	Tarceva	2004 / 2019	6	5%	6%	• Effective targeted treatment for lung cancer • High mortality impact
Gaucher ERTs[3]	Cerezyme	1991 / 2013	5.5	11%	15%	• Enzyme replacement therapy for Gaucher Disease • High mortality impact
Cystic Fibrosis Mucolytics	Pulmozyme	1994 / 2015	5	14%	7%	• Rare and severe disease • Single drug in the class, however limited efficacy
Insulins	Lantus	2000 / 2015	4.5	21%	18%	• Essential treatment for type 1 and some type 2 diabetes patients
GCSFs	Neupogen	1991 / 2013	4	5%	8%	• Bone marrow stimulant following chemotherapy • Limited competition
Atypical antipsychotics	Abilify	1993/2008[4]	3.5	6%	6%	• Therapy for schizophrenia and other psychological disorders • More than 15 competitors in the drug class
Parathyroid Hormone	Forteo	2002/2019	3	8%	-7%	• Treatment for osteoporosis • Single drug in the class, but strong competition from bisphosphonates
Ophthalmic Cyclosporine	Restasis	1994/2019	2	28%	11%	• Treatment for dry eye • Strong competition from low-cost alternative treatments
Adrenergic Inhalants	Advair	2001/2010[5]	2	11%	4%	• Inhaled therapy for asthma and COPD • Chronic treatment, low disease acuity
Anti-TNFs	Humira	1998/2017	2	16%	9%	• Anti-inflammatory immunosuppressant • Multiple low-cost oral classes also used in indications
PDE5 Inhibitors	Viagra	1998/2017[6]	1	32%	1%	• Treatment for erectile dysfunction • Low medically necessity

Table 1: Method of Selecting Drug Classes for Analysis
Source: Health Advances analysis.

Limitations of Analysis

While the resilience score provides a framework to rapidly assess the risk to a given market during a recession, it is not a substitute for a comprehensive analysis.

Small Sample Size

- Only evaluated 13 drug classes which were predominantly mature markets in 2006-2011
- Drug classes were selected because they were less affected by confounding factors, like new market approvals or in-class generic entry

Limited Explanatory Variables

- The resilience score is a composite of readily-available explanatory variables (e.g., efficacy, number of competitors)
- However, other data not available on a product-level basis (e.g., net price increases) could also serve as explanatory variables
- This approach also may not account for market-specific nuances, like evolving treatment paradigms and new clinical practices, innovative diagnostic technologies, etc.

Protective Antibody Therapy: Preventing Future COVID-19 Outbreaks

May 2020

Executive Summary

- COVID-19 vaccines may not be available for at least 12 to 18 months, and possibly as long as five years. More near-term solutions are needed to provide a therapeutic treatment and to achieve prophylactic immunity in high-risk groups.
- Historical evidence from similar viruses such as SARS1 and the H1N1 influenza established precedents for the use of antibodies from convalescent patients to treat or confer immunity
- As accuracy of and access to antibody-detecting diagnostics grow, allowing for widespread testing, countries have initiated nationwide serosurveys which may hold the key to develop plasma-derived antibody therapies
- A significant number of companies and consortia have embarked on this concept and first-movers are entering clinical testing as early as in the second half of 2020
- However, the availability of sufficient amounts of convalescent plasma remains a key challenge. A novel approach, called recombinant anti-coronavirus 19 hyperimmune gammaglobulin or rCIG may provide a longer-term alternative to plasma-derived therapies and can generate scalable polyclonal antibody therapies for millions of patients

Introduction

Viral diseases continue to emerge and represent a serious threat to the global public health. Over the past 20 years, several epidemics such as the severe acute respiratory syndrome (SARS) in 2002/2003 and the H1N1 influenza in 2009 have been recorded. Currently, the world is gripped by the COVID-19 pandemic, triggered by the coronavirus SARS-CoV-2, which seems to be highly contagious and has spread quickly around the globe. At the time of this writing, almost 4MM cases have been diagnosed globally with more than 270,000 deaths[7]. With no specific treatment option currently recommended or available, the pharmaceutical industry has launched an unprecedented effort to provide a prophylactic or therapeutic treatment option.

VACCINES ARE A PROMISING PROPHYLACTIC TREATMENT BUT MAY BE YEARS AWAY

Vaccines are currently regarded as the most promising prevention opportunity and will represent a critical step in the return to normalcy by helping to establish "herd immunity." Vaccines can quickly confer immunity to large numbers of healthy people, preventing rapid spread of the disease and offering protection to high-risk groups by virtue of the immunity of those they meet.

As of May 8th, over 110 different COVID-19 vaccines are in development worldwide[8] and coordinated efforts have been initiated to shorten development timelines. The FDA's Center for Biologics Evaluation and Research (CBER) has pledged to facilitate the development of COVID-19-directed treatment by providing regulatory flexibility, advice, guidance, and technical assistance[9]. In addition, a public-private partnership with the NIH called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)[10] may provide expertise, financial support, and collaborative framework for those companies developing vaccines. Also, novel technologies in vaccine manufacturing can shorten the development timeframe as has been pointed out in a recent Health Advances blog. However, due to the stringent clinical trial requirements and regulations on vaccines, the development time for an effective SARS-CoV-2 vaccine may be more distant than some make us believe. SVB Leerink analyst Geoffrey Porges estimates that a vaccine may not be available for several years[11]. Estimates by Wall Street analysts supported by computer-generated models predict timelines of up to five years. If history is anything to go by, the average development timeline for a new vaccine is even closer to 10 years, and the probability of market entry is as low as 6%[12].

RATIONALE FOR PROTECTIVE ANTIBODIES AS PROPHYLAXIS AND TREATMENT

While there is a distant possibility that vaccine therapies may become available in the nearer-term, it is more likely to assume that projections of 12-18 months until market entry may be too optimistic. Therefore, alternative approaches are needed to treat currently infected moderate-severe COVID-19 patients and to offer prophylaxis to risk-high groups like first responders, and eventually, even to the general population.

> "Convalescent plasma has historically been used therapeutically and for prophylaxis" — as prevention — "typically in times when a new disease, virus, bacteria comes on the scene and we don't have any viral-specific therapies for that new or novel disease," said Dr. Erin Goodhue, executive medical director of the American Red Cross.

Therapeutic antibodies derived from convalescent patients could provide a more timely solution. Therapeutic antibody therapy was first performed over a century ago and is used in clinical practice today for hepatitis A and B, rabies, and respiratory syncytial virus (RSV)[13]. During the last large-scale global pandemic, the 1918 Spanish flu[14], it is believed that antibody therapy greatly reduced the mortality rate. Furthermore, its use has been shown to be effective in coronaviruses similar to COVID-19 such as SARS1[15]. Early results from hospitals using plasma from recovered COVID-19 patients have also shown promise. A small study of 10 severely ill patients treated with convalescent plasma in Wuhan, China, showed improved outcomes over a sex- and age-matched historical control. However, the applications of antibody therapy extend far beyond treatment—antibodies can also be used in healthy patients to *prevent* infection. The applicability of passive immunization through antibodies was also investigated in a widespread indication such as influenza in a recent article, where the authors concluded that the concept

"could be used as pre- or post-exposure prophylaxis to prevent or reduce symptoms or in the treatment of severe influenza infection."[16]

How does antibody therapy work? A convalescent patient's blood contains immunoglobulins, or antibodies, that the patient formed to fight against the coronavirus. The patient's serum or plasma may be transfused directly to another patient, or the coronavirus-specific antibodies can be isolated and concentrated to form hyperimmune globulins which are administered intravenously to confer passive immunity. When the antibodies encounter the virus, they may either target and destroy the virus directly, or stimulate specialized immune cells to attack the virus and offer a therapeutic- or prophylactic benefit.

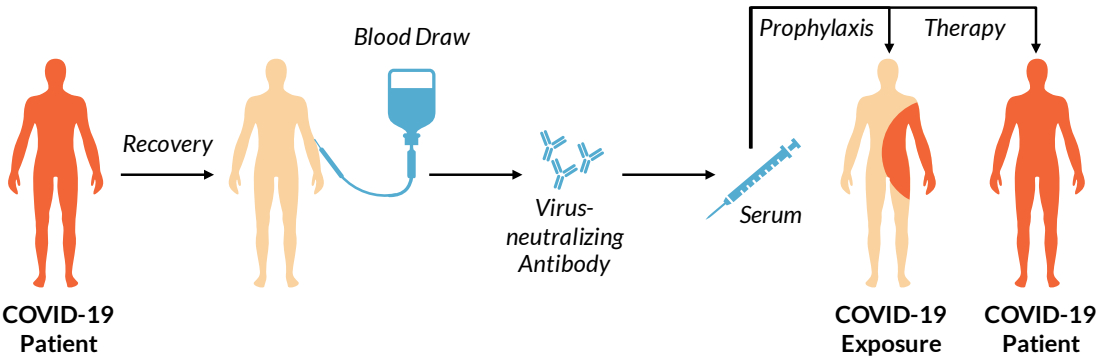


Figure 17: Schematic Principle of Convalescent Antibody Therapy
Source: Health Advances.

WHAT IS REQUIRED TO ENABLE PROTECTIVE ANTIBODY THERAPY?

According to the recent article published in the Journal of Clinical Evaluation[17], "to deploy convalescent serum administration for COVID-19 the following six conditions must be met: (1) availability of a population of donors who have recovered from the disease and can donate convalescent serum; (2) blood banking facilities to process the serum donations; (3) availability of assays, including serological assays, to detect SARS-CoV-2 in serum and virologic assays to measure viral neutralization; (4) virology laboratory support to perform these assays; (5) prophylaxis and therapeutic protocols, which should ideally include randomized clinical trials to assess the efficacy of any intervention and measure immune responses; and (6) regulatory compliance, including institutional review board approval, which may vary depending on location." So, where do we stand on these six conditions across geographies?

- With almost 4MM[18] COVID-19 patients have been registered worldwide with varying degrees of patient recovery rates, ranging between 94% for China to 17% for the US, reflecting different approaches to testing, patient tracing, and the evolutionary stage of the pandemic in the respective local region, among other factors. This patient pool hasn't gone unnoticed and the American Red Cross[19] together with the FDA has started an appeal to collect convalescent plasma. Similar initiatives can be observed in Europe.

- Worldwide, more than 110MM[20] blood donations are collected annually, about 100MM of which as whole blood and about 12MM donations are plasma collected via apheresis. Processing this amount of blood donations suggests that the necessary infrastructure is in place to effectively and safely collect convalescent COVID-19 plasma. With about 25% of global blood donations processed in Europe, the old continent may be slightly better positioned compared to the rest of the world
- Assay availability is critical to accurately identify convalescent donors and over the last months around 60 tests[21] have been approved by different regulatory agencies. While most of the tests are PCR-based with focus on the identification of COVID-19 patients, antibody tests have also become generally available across all geographies but questions on reliability continue.
- The availability of testing facilities has been a point of debate during the COVID-19 pandemic and a recent blog from Health Advances highlighted the shift towards decentralized testing capabilities to allow for a faster response to a pandemic. However, during the COVID-19 crises, the installed base of testing capacity has never been questioned, rather the availability of the appropriate assays.
- At the time of writing, more than 40 clinical studies have been initiated in all major geographies applying an antibody focused approach, and 14 of these use convalescent COVID-19 plasma[22] but given the early stages of the clinical development, it will still require additional scientific and clinical confirmation before robust protocols for treatment and prophylaxis have been established.
- Regulatory agencies in the US[23], Europe[24] and China[25] have been quick to realize the beneficial potential of IgG antibody therapies and have established directives that govern all aspects from collection to administration of these therapies, however at present focused on a therapeutic application.

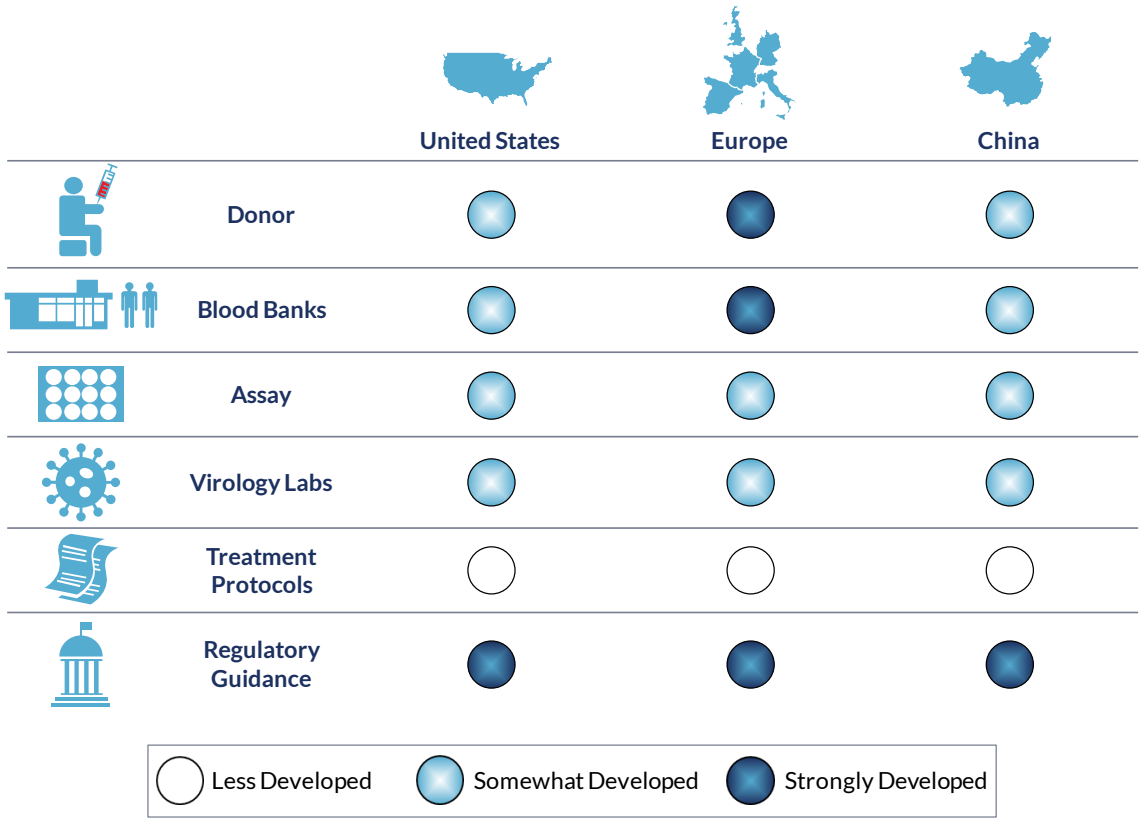


Figure 18: Six Test Assessment by Geography
Source: Health Advances analysis.

Applying the six tests to the United States, Europe and China, suggests that all three regions should be well-positioned to manufacture and distribute convalescent-plasma derived antibody therapies. However, one glaring gap is detailed treatment protocols do not exist in any geography but should become available, together with the approval of the corresponding prophylactic and therapeutic options.

THERAPIES IN DEVELOPMENT

At the time of writing, more than 300 COVID-19 focused therapeutics are in development and more than 40 projects involve antibody therapies, including recombinant- and plasma-derived approaches.

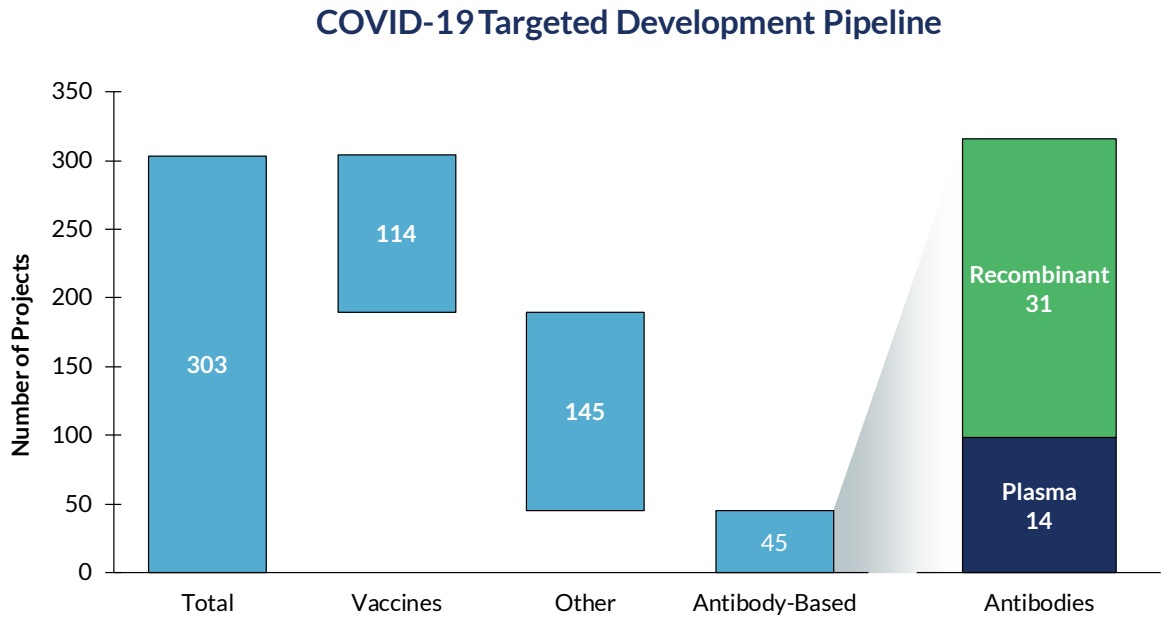


Figure 19: Six Test Assessment by Geography
Source: Health Advances analysis, Pharmaprojects.

Many of the plasma-focused development projects involve collaborations across multiple geographies. Grifols SA, the Spanish drugmaker, is teaming up with the U.S. Biomedical Advanced Research Development Authority, the U.S. Food and Drug Administration and other Federal public health agencies to develop plasma-based therapies. Grifols and the health agencies will process the collected plasma into a hyperimmune globulin, or HI-G, and support the necessary preclinical and clinical studies to determine if anti-SARS-CoV-2 HI-G therapy can be used to treat COVID-19. The company said it is volunteering its resources in plasma collection using FDA-approved plasma donor centers. It will test and qualify donors with the help of the other health agencies and process plasma into HI-G and conduct studies to determine whether HI-G made from the plasma of recovering donors can be a viable treatment for the disease. An even broader consortium has been established between Australia's CSL, Japanese Takeda, and European firms Biotest, BPL, LFB, and Octapharma to develop a plasma-based therapeutic. The global nature of the alliance has been established with the specific goal to establish sustainable and scalable infrastructure for the manufacture and distribution of plasma-based therapies. However, with the required number of IgG-antibodies unknown to reach immunity in patients, the availability of sufficient plasma donations remains unclear.

A novel approach, that could directly address potential supply issues of plasma based therapies, is called rCIG (recombinant anti-coronavirus 19 hyperimmune gammaglobulin) and is pursued by GigaGen. This approach uses single-cell sequencing to "capture and recreate" whole libraries of antibodies from recovered COVID-19 patients. The company can then choose which of those antibodies to turn into recombinant polyclonal antibody treatments in a method that does not rely on collecting vast amounts of plasma from many donors. Although rCIG could be given as a prophylactic, it is seen as a therapeutic since

it must be given to patients intravenously. This method is much more scalable than plasma-based methods, since one person's B cell repertoire can be used to generate a drug that treats millions of patients. "The ability of the platform to capture and replicate complete antibody libraries from recovered patients … has the potential to overcome challenges related to supply shortages, which is an ongoing problem for plasma-based therapies… " the company said in a recent press release[26]. Additionally, due to their recombinant nature, GigaGen's recombinant polyclonal therapies have a decreased risk of contamination and are consistent from batch to batch, enabling a controlled dosing protocol. As promising as this sounds, rCIG will not enter clinic trials until early 2021.

CONCLUSIONS

Plasma derived antibodies have been used throughout the history of pandemics and may be a valid treatment option as they can be readily available and have long played a role in conferring immunity to viruses. The plasma-based therapy development represents a near-term opportunity, based on the existing collection, processing and delivery infrastructure. Additionally, regulatory paths have been established by the FDA, EMA and NMPA that will put the development on a reliable regulatory path. Questions remain as to whether the antibody titer required to achieve COVID-19 immunity and the duration the COVID-19 specific immunity can be maintained. Newer innovations such as rCIG derived antibodies may be a longer-term option but have the capability to circumvent any potential shortages of much needed convalescent plasma while offering the possibility of significant production scale-up.

Rapid Responders: How Innovative Technologies are Accelerating Development of New Vaccines

April 2020

Executive Summary

- Within three months of the first cases of COVID-19 (SARS-CoV-2) appearing in China, there are already more than 40 novel drugs in the US pipeline to target COVID-19, and five novel vaccines in clinical trials worldwide
- Newer technologies such as nucleic acid-based vaccines and single cell sequencing have enabled faster lead identification times than in previous pandemics
- A diversified pipeline portfolio of fast-moving innovative products and long-term traditional vaccines with other containment strategies like shelter in place and social distancing, can provide a balanced short and long-term strategy to bring pandemics under control
- Companies with platforms that can be more readily customized such as mRNA vaccines, antisense oligonucleotides (ASOs) and RNAi therapies can move through development faster, but they are often smaller biotech startups who will require more federal financial assistance in early pre-pandemic stages when risk is still high
- Federal assistance programs need to be developed and tailored to provide R&D funding to companies at pre-pandemic stages to encourage rapid mobilization of resources to bring new products to clinical trial as quickly as possible

Innovative Technologies Driving Faster Development

As we approach the three-month mark since COVID-19 cases began spreading throughout China, it may feel like there's no hope in sight for getting new drugs and vaccines to the frontlines to bring the pandemic under control. In reality, biopharma companies are moving faster than in previous pandemics. As of early April, there are approximately sixty COVID-19 drugs in the US pipeline, with about 80% of those being novel vaccines and drugs specifically tailored to fighting the novel coronavirus. Of the novel drugs in development, approximately half of those are vaccines, and a quarter are neutralizing antibody therapies that could be used as both prophylaxis or treatments. As of April 9th, there are already five vaccines of various technological modalities in clinical trials worldwide, two of which are in the US (see Table 1). Any of these candidates, if successful, could have a significant impact on bringing the COVID-19 outbreak under control and potentially could be a foundation for a potential future response if or when new coronaviruses surface.

Company/Institute	Modality	Phase	Trial Start	Trial Country
深圳市免疫基因治疗研究院 SHENZHEN GENO-IMMUNE MEDICAL INSTITUTE	Artificial Antigen-Presenting Cells	Phase I	February 15	China
moderna	mRNA Vaccine	Phase I	March 16	US
CanSinoBIO	Adenoviral Vaccine	Phase I	March 16	China
深圳市免疫基因治疗研究院 SHENZHEN GENO-IMMUNE MEDICAL INSTITUTE	Lentiviral Vaccine + Antigen-Targeting Cytotoxic T Lymphocytes	Phase I	March 24	China
inovio	DNA Vaccine	Phase I	April 6	US

Table 1: Vaccines in Clinical Trials for COVID-19 Worldwide as of April 9th
Source: Health Advances analysis, PharmaProjects, Le 2020 Nat Rev Drug Discov, company press releases.

Health Advances set out to understand which US companies are moving quickly in developing novel coronavirus-targeting drugs and what factors are contributing to their development timelines. In our analysis, we focus on companies that we refer to as "Rapid Responders" – companies that quickly mobilized to initiate R&D programs of new COVID-19 vaccines and therapeutics, and are predicted to reach clinical trial by this summer. We performed an in-depth analysis of factors including platform technology, access to capital, federal assistance, and clinical development resources. Surprisingly, we found that the primary driving factor contributing to a rapid response was innovative technology platforms. Below, we provide illustrative examples of US companies that are representative of larger trends in the global pipeline (see Table 2).

Company	Modality	Status	Mechanism of Action	Time from Project Start to Leads	Time from Lead to Trial
moderna	mRNA Vaccine	Phase I	mRNA encoding viral Spike protein is delivered to individuals, host cells produce protein, triggers immune response, and confers immunogenicity	25 days	38 days
inovio	DNA Vaccine	Phase I	DNA encoding viral Spike protein to induce immune response delivered using a hand-held injection and electroporation device	14 days	74 days
REGENERON	Virus-Neutralizing Antibodies	Preclinical	Neutralizing antibodies isolated from immunized mice with humanized immune system	43 days	Est. 60 days
Lilly AbCellera	Virus-Neutralizing Antibodies	Preclinical	Single cell screening and sequence to identify neutralizing antibodies from a recovered COVID-19 patient	11 days	Est. 60 days
janssen	Adenoviral Vaccine	Preclinical	Recombinant adenoviral vectors used to deliver genes instructing host cells to produce viral antigens for immunogenicity	72 days	Est. 180 days

Table 2: Overview of Key Rapid Responders, Technologies and Development Timelines
Source: Health Advances analysis, PharmaProjects, Le 2020 Nat Rev Drug Discov, company press releases.

Moderna gained notoriety with the first novel coronavirus vaccine to begin clinical trials. What enabled Moderna to progress so quickly? Compared to big pharma giants, it may not have had access to as large sources of capital or decades of experience in large, global clinical trials. What it did have, was a unique technology platform that enabled it to bypass traditional vaccine development bottlenecks. Moderna's vaccine platform is based on delivering mRNA to patients, rather than protein or viral antigens as in a traditional vaccine. The mRNA delivered to patients contains the genetic instructions for the host's cells to make the viral antigen themselves, which will trigger an immune response and confer immunogenicity. Compared to a traditional vaccine, this provided three major advantages:

- ***Faster:*** Sequence design of the mRNA molecule is fast and done *in silico* and took only two days to generate a mRNA vaccine candidate sequence following the release of the novel coronavirus genome sequence.
- ***Cheaper:*** mRNA manufacturing is cheaper and more streamlined than recombinant protein or viral production used for traditional vaccines since there is no need to optimize production for each new mRNA molecule, and production can be scaled rapidly on existing infrastructure.

- ***Safety:*** The mRNA vaccine platform itself is already considered safe for use in humans since it has nine other mRNA-based prophylactic vaccine candidates in clinical trials. This allowed the rapid adaptation to the new sequence, without the long process of comprehensive preclinical safety profiling in rodents.

In comparison, a traditional protein antigen or adenoviral-based vaccine will generate a new protein or adenovirus antigen for each new product, and each new antigen will need to both have production optimized and scaled, and will also require safety and efficacy testing in animal studies. Moderna was able to bypass that long process due to its platform, which enabled the company to generate a lead in just 25 days and enter clinical trials thirty-eight days after that on March 16th. This was only sixty-three days after the death of the first COVID-19 patient in Wuhan. If the eight-week trial shows signs of success, Moderna would be on track to start immunizing front-line healthcare workers in the fall of 2020.

Inovio also rapidly mobilized its DNA-based vaccine platform and made an early move in generating a vaccine against the novel coronavirus. Similar to Moderna, using a nucleic acid-based platform enabled a quick product design based on sequence, and a streamlined production process. In contrast to RNA vaccines that can be delivered with only the assistance of liposome-based agents, Inovio's DNA vaccine must be delivered with a handheld device that injects the DNA and simultaneously electroporates the host cells to promote DNA uptake. This platform required efficacy studies in rodents, leading to a clinical trial start time three weeks later than Moderna.

Both Moderna and Inovio's platforms rely on cost-effective and scalable synthesis of long synthetic nucleotides that can be used as a vaccine. The artificial synthesis of DNA and RNA fragments long enough to encode full antigen-encoding genes (i.e. ~1 kb and larger) was not readily possible or scalable until the last decade. Continued technological improvements in DNA and RNA *de novo* chemical synthesis, and RNA *in vitro* transcription, have allowed these fragments to be produced in a relatively cheap and scalable fashion that have enabled these vaccine modalities to be possible. Moreover, next generation sequencing technologies enabled the SARS-CoV-2 viral genome to be reported in a mere number of days once it was isolated in China, which allowed for rapid *in silico* sequence-based design of DNA and RNA vaccines. Together, these recent advances in nucleic acid synthesis and sequencing are major drivers of enabling these new fast-moving vaccine platforms.

In addition to nucleic acid-based vaccines, other players are bringing in newer technologies to speed up the development of more traditional antibody-based modalities. AbCellera, in collaboration with Lilly, is using a novel platform of single cell immune cell profiling and sequencing to screen a blood sample from a recovered COVID-19 patient to isolate and clone coronavirus-neutralizing antibodies. They were able to produce 500 candidate coronavirus neutralizing antibodies in only eleven days from receiving the blood sample. The strength of the AbCellera platform is that it allows the best 'developer' of virus neutralizing antibodies (the human immune system) to be the chosen platform. Using a single cell screening and sequencing platform allowed them to bypass a lengthy process of monoclonal antibody production in rodents and subsequent humanization engineering, a process that would have taken closer to eleven months rather than eleven days. This approach effectively saved months in the development process. Additionally, their partnership with Lilly allows them to take advantage of Lilly's expertise in antibody manufacturing and potential manufacturing scale up capabilities. Through the partnership, AbCellera

hopes to be in clinical trials and enrolling patients to start testing its coronavirus neutralizing antibodies this summer.

Regeneron is also using innovative technologies to speed up the typically lengthy process of developing neutralizing antibody therapies. Regeneron's VelocImmune platform utilizes mice that have had significant regions of the genome encoding the building blocks of antibodies replaced with human counterparts, effectively creating mice with a 'humanized' immune system. This means that antibodies generated in these mice in response to a viral antigen are already 'human' antibodies by sequence, and compatible with the human immune system. While the process of isolating, culturing and screening mouse immune cells and the subsequent manufacturing scale-up is still a very lengthy and expensive one, this technology does enable bypassing the arduous step of needing to 'humanize' a mouse antibody by sequence engineering. This removes one key bottleneck, saving precious time. Using their coronavirus-fighting mouse hybrids, Regeneron was able to identify lead antibodies 40 days after initiating R&D and anticipates beginning clinical trials this summer.

As a benchmark, Johnson & Johnson's Janssen, a global leader in vaccines, rapidly initiated a R&D vaccine program to tackle novel coronavirus in January, being one of the first responders when the number of cases worldwide was still less than 10,000. While Janssen's more traditional adenoviral-based vaccine program is tried and true, this traditional technology platform comes at a significant disadvantage – longer time to clinical trials. Despite being one of the first rapid responders to initiate a COVID-19 program, they do not expect to reach clinical trials until September 2020.

At this point it is not clear, which technology will produce a prophylactic vaccine in time to address the significant clinical need. In order to ensure that the right product comes to market in the right timing, industry must have multiple shots on goal. Both traditional and more innovative technologies must be pursued in order to mitigate the impact of the COVID-19 and future pandemics. While newer innovative technologies may be able to respond faster in a crisis, they are also less proven on efficacy and safety in the long-term. At this point, we do not know whether the most efficacious and safe solution to ending COVID-19 may indeed be a traditional vaccine that takes one year to develop. However, even if faster-moving products would end up being only half as efficacious or have safety profiles that could limit their use, they may still be a viable solution in the near-term until other more efficacious or safer products become available. Leveraging multiple traditional and innovative technologies due to their advantages simultaneously is the best way to balance these risks and the only way to ensure that the US is better prepared for the next coronavirus outbreak.

As can be seen in Table 3, more innovative technologies are viewed as more attractive because of their lower R&D costs and shorter development times; while more traditional vaccine approaches are viewed as having greater proven efficacy. Pursuing multiple avenues simultaneously allows for balancing short- and long-term risks and needs and increases the probability of a response that could mitigate another crisis situation like that seen in New York from happening.

Company	Modality	Innovative Technology	Development Time	Estimated R&D Cost	Risk Based on R&D Initiation Timing	Historically Proven Efficacy
moderna	mRNA Vaccine					
inovio	DNA Vaccine					
Lilly AbCellera	Neutralizing Antibodies					
REGENERON	Neutralizing Antibodies					
janssen	Adenoviral Vaccine					

Table 3: Comparison of Advantages, Disadvantages and Relative Risks of Profiled Key Technologies
Source: Health Advances analysis, FiercePharma.

Getting the Timing Right: Mitigating R&D Risk Pre-Pandemic to Hasten Novel Vaccine and Therapy Development

During the SARS, Ebola, Swine Flu and Avian Flu outbreaks, the time from outbreak onset to clinical trials of candidate vaccines was one to two years on average (see Table 4). In the case of SARS, by the time a vaccine was available, the pandemic had largely died out and clinical trials could not be completed. Without sufficient patients and disease burden to test efficacy in a clinical trial, programs were abandoned. That left companies that invested in SARS with no return on their investment. Since the vaccine was never tested, there was no vaccine that could be sold to national stockpiles, and the R&D costs were shouldered exclusively by their investors.

Year	Pathogen	Approximate Time from Outbreak to Vaccine Candidate for Clinical Trial
2002-2004	SARS (SARS-CoV-1)	24 months
2005	H5N1 Influenza (Avian Flu)	24 months
2009	H1N1 Influenza (Swine Flu)	9 months
2014-2016	Ebola	12 months
2019-2020	Novel Coronavirus (SARS-CoV-2)	2 months

Table 4: Comparative Examples of Time from Outbreak to Clinical Trial in Previous Pandemics
Source: Health Advances analysis, FiercePharma, Coalition for Epidemic Preparedness Innovations.

Being able to predict pandemics is an impossible feat, and poses a critical question to companies: When is the right time to start investing in expensive R&D on a product to help minimize the impact of a pandemic? Clearly the answer is before it reaches the level of infection and mortality rates as seen with COVID-19. But how much earlier is the question. The transmission rate of COVID-19 would suggest that the investment needs to be made before the virus follows the business and personal travel patterns between the country of origin and the US. The COVID-19 experience showed that it can be very short – only a few months.

How does industry turn on a dime and gear up to meet the challenge of a virus that can go pandemic in a matter of mere months? There are two major factors to consider:

- ***Leveraging innovative technologies***: Encourage companies with streamlined platforms that require relatively less time in development by using safe and established customizable platforms like mRNA vaccines, antisense oligonucleotide (ASO) therapies, or RNAi therapies to pursue vaccine development.
- ***Resource companies with those technologies:*** Provide federal assistance to biotech companies with these technologies to help fund R&D efforts to offset the risk associated with missing the window of commercial opportunity (products that are approved after the pandemic is over) or a non-reoccurring pandemic (the virus is contained locally and vaccines are not needed) or the vaccine failing in clinical trials.

Moderna is a case study of how leveraging innovative technology and providing federal resources could enable a rapid response. Moderna did not have to assume as much financial risk as a traditional vaccine maker because comparatively, repurposing its existing mRNA vaccine platform and scaling nucleic acid

synthesis is not as expensive as development of a vaccine based on recombinant proteins or viral vectors. Moderna also had a close collaboration with the National Institute of Allergy and Infectious Disease (NIAID), which provided assistance for both R&D and phase I clinical trials. Because of this, Moderna was the first of the rapid responders to announce the beginning of its program on January 11th, when there was fewer than 100 known cases in China, and only one death. If COVID-19 had not become a pandemic, Moderna would not be as financially impacted as a traditional vaccine maker was at the end of SARS. Just last week, BARDA committed $483 million in assistance to help Moderna fund phase II-III clinical trials and vaccine manufacturing scale-up. With mitigated financial risk and federal assistance, Moderna made an early bet, and the NIAID partnership allowed senior management to make a shift in their R&D that has the potential to have a decisive impact on controlling this outbreak.

Table 5 tracks the project start dates and the estimated clinical trial start date of the rapid responders that Health Advances analyzed. Moderna took action before the disease had spread to the US. With the support of NIAID, their management may have felt more comfortable in redirecting valuable R&D resource to a virus which may or may not cross the Pacific Ocean. At that point, there were only sixty confirmed cases worldwide.

Company	Modality	Project Start	Confirmed Cases at Project Start	Start of Clinical Trial
inovio	DNA Vaccine	January 10	WW: 59 cases US: 0 cases	April 6
moderna	mRNA Vaccine	January 11	WW: 59 cases US: 0 cases	March 16
janssen	Adenoviral Vaccine	January 29	WW: 6,067 cases US: 5 cases	Est. September
REGENERON	Neutralizing Antibodies	February 4	WW: 20,615 cases US: 11 cases	Est. June-July
Lilly AbCellera	Neutralizing Antibodies	March 12	WW: 125,497 cases US: 1,312 cases	Est. June-July

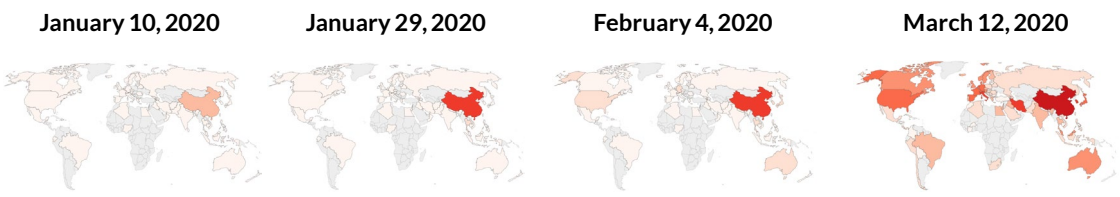


Table 5: Timelines of Highlighted Rapid Responders Initiating Projects at Various Stages of the Novel Coronavirus Outbreak
Source: Health Advances analysis, OurWorldInData European Center for Disease Prevention and Control.

If a rapidly deployable funding mechanism had been in place, other companies may not have waited to redirect their R&D resources to COVID 19 until the disease had passed tens or hundreds of thousands of

cases worldwide and had been detected in the US. Starting at a riskier time (before the disease has spread outside China) could potentially have resulted in their clinical trials starting three weeks earlier in May. With this type of funding mechanism, companies like AbCellera may have been in clinical trials as we write this blog. Presumably, there are numerous other companies with innovative potential solutions to tackle coronavirus that could have been encouraged to participate in R&D efforts but saw the risk as too high to become engaged, or could have started R&D weeks to months earlier.

Why is a funding mechanism like this so important? Innovative technologies like mRNA vaccines, antisense oligonucleotide (ASO) therapies, and RNAi therapies that move through R&D faster are generally developed in smaller biotech companies that are more cash strapped than big pharma. As a point of comparison, Janssen also announced initiation of its coronavirus-targeting vaccine in January when the pandemic was still restricted to China with less than 10,000 cases reported. Given their cost-intensive, more traditional vaccine development platform, this was a large financial risk at a time where it was not clear that the vaccine would have a commercial market. This is a risk that could only be taken by a large pharmaceutical company.

There are federal assistance programs that exist today to support the manufacturing of vaccines for pandemics. Unfortunately, they do not address the core issue of offsetting R&D costs. Currently, the US Department of Health and Human Service's Biomedical Advanced Research and Development Authority (BARDA) will buy vaccine stockpiles left over at the end of a pandemic. This program has two major issues:

- It does not provide research grants to offset the early R&D costs, which is critical to smaller biotech companies who often are cash strapped.
- It only provides a revenue stream for commercialized products. Companies who take the risk but cannot bring a product to market have no way to recoup their investment. The possible risk of a product not panning out or a disease not becoming a pandemic makes the decision very difficult for companies to convince their stakeholders to initiate programs.

How can we ensure that the R&D efforts for the next potential pandemic start at day 0 rather than the first patient in the US? Companies need to be incentivized to initiate R&D early on in disease outbreaks before a pandemic is even called. US federal agencies such as BARDA should create accelerated federal grant programs that provide emergency grants to appropriate companies that initiate R&D at early signs of an epidemic. With such new initiatives in place, R&D could be started when the risk for the individual company is still high, but has the potential for greatest clinical impact. The potential consequences of not taking early action will continue to have a drastic impact on public health, healthcare costs and the economy.

Summary

As the number of confirmed COVID-19 cases surges towards 2 million worldwide, new vaccines and coronavirus-targeting therapies are urgently needed to get this pandemic under control. While the situation may seem bleak, pharma and biotech companies alike are moving faster than ever before to

develop new products. Among the fastest responders, newer innovative technology platforms like mRNA vaccines could proceed through a streamlined response, but these companies may also require federal funding to offset R&D costs in order for projects to be initiated early enough to meaningfully change mortality outcomes such as those we are seeing in this pandemic. Federal assistance to offset early R&D efforts, especially those with fast-moving technologies such as mRNA vaccines, ASOs or RNAi therapies, will assist in enabling a rapid response and allow a better response to the next coronavirus that may materialize into a pandemic. The US has the ability and resources to enable industry to move on vaccine development earlier. Now we need to ensure that federal programs are developed and put in place to encourage earlier participants to pivot their R&D efforts so that we can get into clinical trials earlier for the next virus that may become a pandemic.

Conclusion

COVID-19 is creating extraordinary uncertainty and turbulence for the biopharma sector, resulting in both risks and opportunities.

The risks facing biopharma are numerous: the recession created by the economic shutdowns will likely depress revenues and may limit access to capital. Biopharma is also facing operational challenges, including supply chain and clinical development disruptions. In our analysis, we focused on the revenue impact created by prior recessions and showed that, in the past, these effects were highly uneven and depended on the product mix of individual companies. Some products are more resilient and fare better in recessions, while others are more volatile and vulnerable to downturns. Regardless, biopharmaceutical companies would be well served to strengthen adherence and market access programs to protect against patient leakage, the risk of which is greatly elevated as patients and payers come under financial strain.

While there are numerous risks to navigate, COVID-19 has also created opportunities. Foremost among these is the unprecedented global demand for COVID-19 vaccines and therapeutics. Not only is the commercial opportunity significant, but biopharmas developing these products are benefiting from government subsidies and expedited regulatory review programs that are accelerating timelines and lowering costs. Here, we show that novel platforms (e.g., GigaGen's recombinant antibodies, Moderna's mRNA vaccine) are showing promise and may enable biopharmas to accelerate development and/or rapidly scale production of new treatments far beyond the near-term focus of containing COVID-19.

COVID-19 has created a fertile test bed for these novel platforms, allowing them to be tested and potentially validated at a pace and scale heretofore unseen. It is too early to say whether any of these new platforms will be successful. Less efficient but tried-and-true modalities and techniques may yet yield more and/or better therapeutics for COVID-19. Regardless, biopharma's broad and robust pursuit of treatments for the pandemic is a testament to the vibrancy of the industry. At the very least, the diverse array of approaches improves the odds that we will find effective COVID-19 treatments. Furthermore, what we are learning about these platforms will surely redound to the benefit of other conditions where these approaches may be applied. In the midst of this terrible pandemic, that is something to celebrate.

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About Health Advances

Health Advances is a strategy consulting firm that focuses exclusively on the healthcare industry. We are scientists, clinicians, and business professionals who share a passion for supporting commercialization and driving adoption of innovations that improve healthcare. The firm employs over 170 full-time professionals in four main offices. We help clients realize growth opportunities worldwide for healthcare technologies, products and services. Our consultants partner with senior executives and investors on their highest-stakes strategic decisions. We not only understand the complexities of each technology and disease state, but also appreciate the client's context within the entire healthcare ecosystem. Our consultants understand regulatory constraints, referral patterns, and economic incentives that can impact the adoption of products and services. As a result of our deep knowledge of the complexities of the healthcare sector, we dig deeper, think broader, and reach further. This enables Health Advances to provide our clients with innovative perspectives and actionable insights that help them make more confident strategic business decisions that capitalize on their company's growth potential.

Sources and Notes

SOURCES

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NOTES

[1] Based on weighted average price per prescription for 50 top-selling brand-name specialty and non-specialty drugs. Specialty drugs include four of the following seven characteristics: cost at least $6,000 per year, be initiated or maintained by a specialist, be administered by a health care professional, require special handing in the supply chain, be associated with a patient payment assistance program, be distributed through nontraditional channels (such as a specialty pharmacy), or require monitoring or counseling either because of significant side effects or because of the type of disease being treated.

[2] Patents expiring in 2025 are related to manufacturing techniques.

[3] Note that Genzyme also struggled with manufacturing challenges during this period, but sales growth still persisted.

[4] Clorazil was an early atypical psychotic. Generics for it were already available by 1990, but those effects were already established in the market place.

[5] Inhaled formulations of these drugs have been difficult to replicate and generics did not enter the market in this period.

[6] Lower dose generic versions of Viagra (sildenafil) became available in 2012 but were only approved for pulmonary arterial hypertension. This analysis only looks at PDE5 inhibitors that treat erectile dysfunction (ED). Note: HER2 = human epidermal growth factor receptor 2; EGFR = epidermal growth factor receptor; GCSF = growth colony stimulating factor; ERT = enzyme replacement therapy. TNF = tumor necrosis factor; PDE5 = phosphodiesterase type 5. Adrenergic inhalants have historically been difficult to replicate into generics.

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