

Pharmaceuticals & Medical Products Practice

Refueling the innovation engine in vaccines

Vaccine development has slowed over the past five years, but changes to investment strategies and a shift in focus to more technical and complex vaccines could renew the innovation engine.

by Tara Azimi, Michael Conway, Jennifer Heller, Adam Sabow, and Gila Tolub



From a global public-health standpoint, vaccines are considered some of the most important inventions in human history. Some notable achievements of vaccines include the eradication of smallpox and the near eradication of poliovirus. Approximately 300 million people died of smallpox between 1900 and 1980, and millions more were disfigured; however, by 1979, vaccination programs had completely wiped out the disease.¹ In 1988, at the onset of a global campaign to end polio, there were 350,000 new cases per year; nearly 30 years later, only 22 cases were reported,

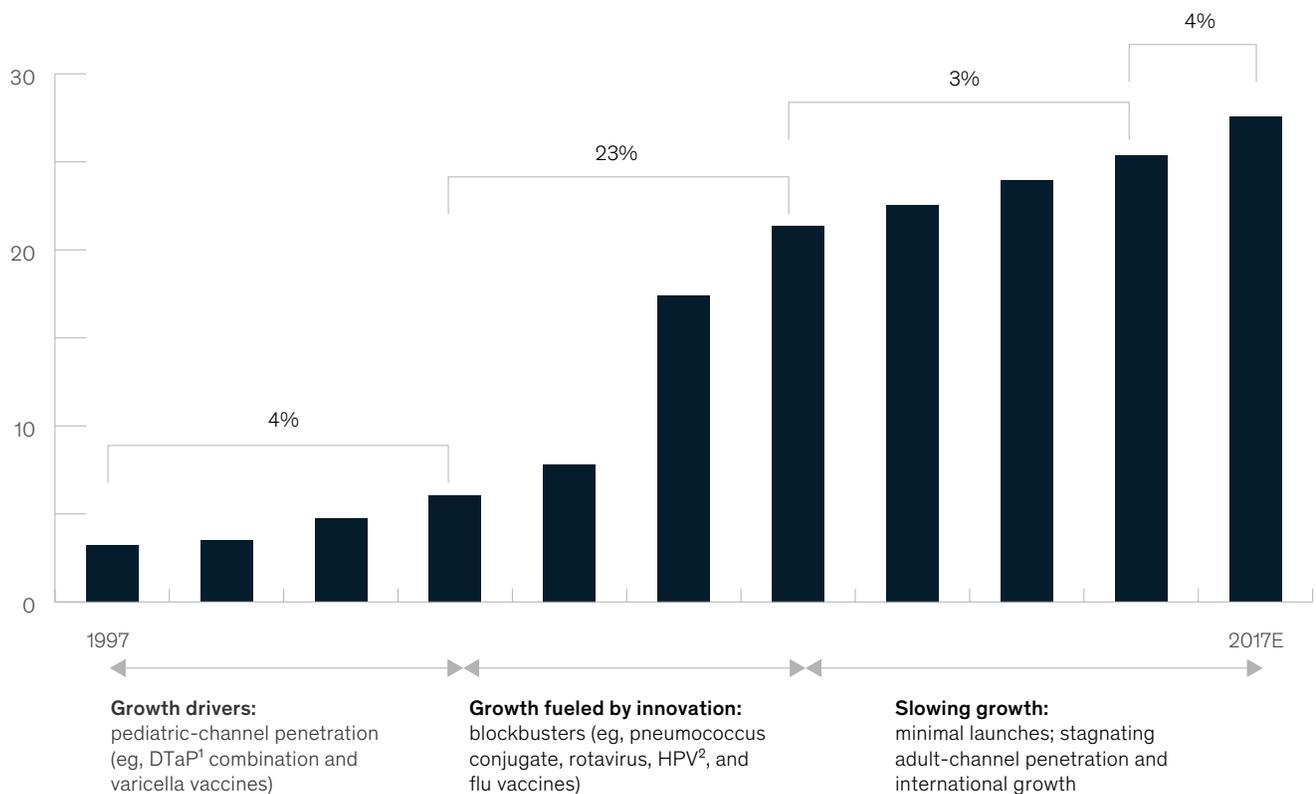
and those were in war-stricken areas where immunization was not possible.²

The past 20 years have seen a rejuvenation of innovation in vaccines, including vaccines for pneumococcus, rotavirus, human papillomavirus (HPV), and varicella. Indeed, in the 2017 annual letter, the Bill & Melinda Gates Foundation reported that 122 million children's lives had been saved since 1990—and that vaccines were the biggest reason for this decline in childhood deaths.³

Exhibit 1

After a period of rapid growth, vaccine sales have slowed in recent years.

Global vaccine sales, biennial, 1997–2017E, \$ billion



¹Diphtheria, tetanus, and pertussis.

²Human papillomavirus.

Source: EvaluatePharma, Evaluate, September 2018, evaluate.com; McKinsey analysis

¹ Frank Fenner et al., *Smallpox and its eradication*, Geneva, Switzerland: World Health Organization, 1988, apps.who.int.

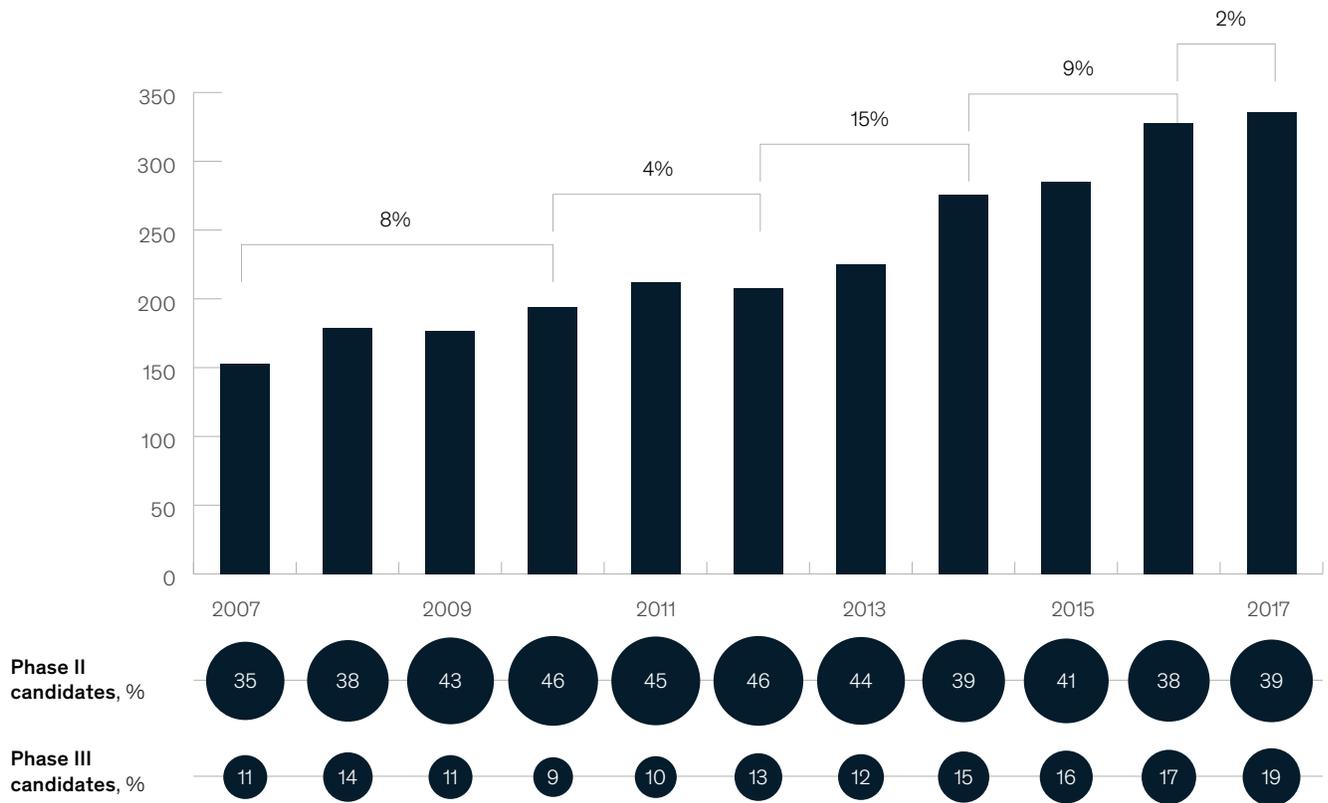
² Poliomyelitis, World Health Organization, March 1, 2019, who.int.

³ Bill Gates and Melinda Gates, "Warren Buffett's best investment," Gates Notes, February 14, 2017, gatesnotes.com.

Exhibit 2

The number of infectious-disease-vaccine programs in development has flattened over the past two years.

Phase I infectious-disease vaccines in development globally,¹ 2007–17, number of products



¹From Phase I to preregistration.

Source: Pharmaprojects, Pharma Intelligence by Informa, September 2018, pharmaintelligence.informa.com; McKinsey analysis

These statistics are in line with the historically high growth rate of the vaccine industry—12 to 15 percent year on year over the past two decades—which is double the rate of the rest of the pharmaceutical industry.⁴ In the past ten years, the number of vaccines in the pipeline has also doubled, to 336 vaccines in 2017.⁵ And while vaccines have mostly focused on disease prevention to date, we expect them to play an increasing role in treatment (for example, treatment vaccines for HPV and hepatitis B) and thus have even greater impact in the future.

However, we have seen four signs of slowing innovation over the past five years:

1. Revenue growth has slowed to below 5 percent in the past five years (Exhibit 1).
2. We are now seeing a flattening development pipeline (Exhibit 2), with the share of growth from new vaccines launched down from almost 50 percent in 2011 to less than 15 percent in 2017—the lowest level in 20 years (Exhibit 3).⁶

⁴ EvaluatePharma, Evaluate, September 2018, evaluate.com.

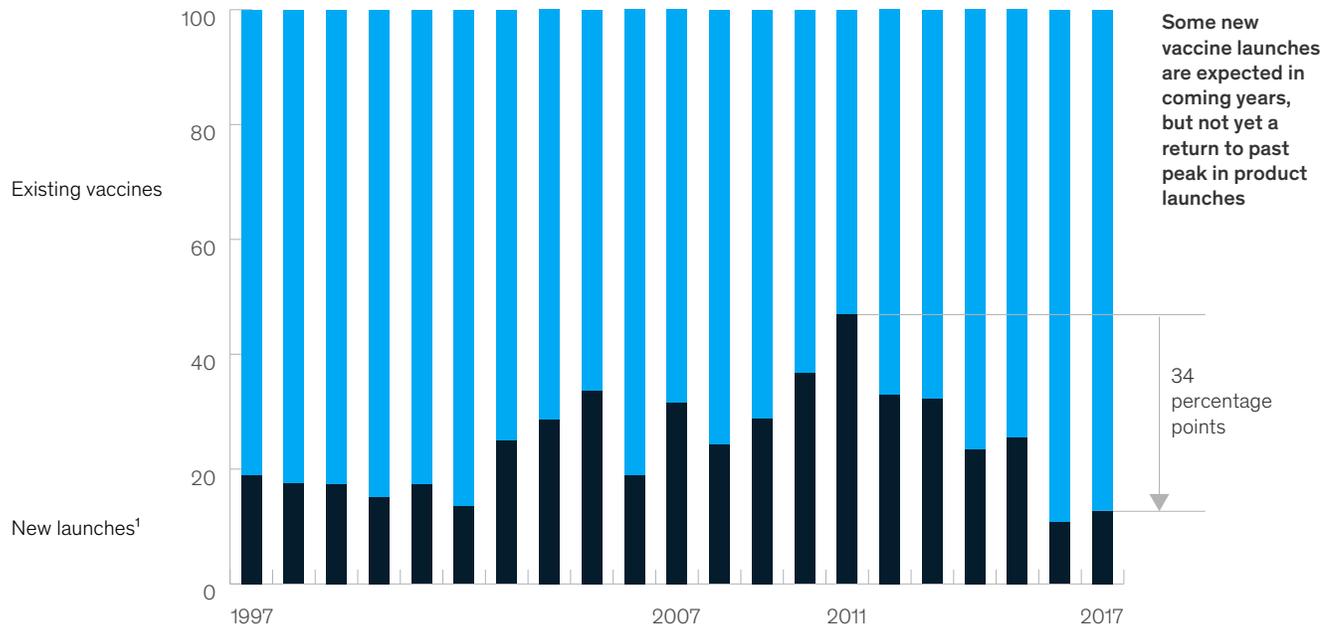
⁵ Pharmaprojects, Pharma Intelligence by Informa, September 2018, pharmaintelligence.informa.com.

⁶ EvaluatePharma.

Exhibit 3

The proportion of sales from new vaccines has declined in recent years.

Global vaccines sales, 1997–2017, %



¹Defined as any vaccine that received US Food and Drug Administration approval in preceding 5 years.
 Source: EvaluatePharma, Evaluate, September 2018, evaluate.com; McKinsey analysis

3. We are recording higher attrition rates for vaccine-development programs relative to other biologics, with “fewer shots on goal,” meaning fewer vaccine candidates are advancing to clinical studies (Exhibit 4).⁷
4. There are remaining unmet needs cutting across multiple categories of vaccines, including diseases endemic to high-income regions (such as HIV and norovirus) and those endemic to low-income regions (for instance, tuberculosis and malaria).

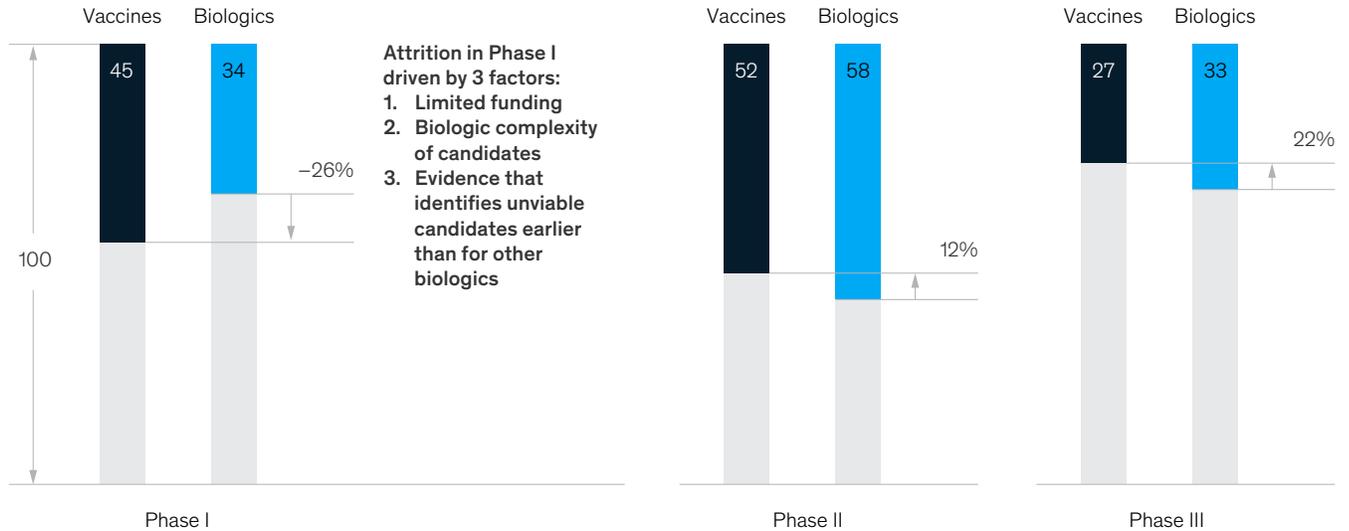
Historically, the “Big Four” global vaccine manufacturers (that is, GlaxoSmithKline, Merck,

Pfizer, and Sanofi) have driven most innovation. However, in the past five years, their pipeline growth has been flat, and the majority of new programs in the pipeline have been driven by emerging-market players with “me too” vaccines (that is, vaccines undifferentiated from those already on market) and by smaller biotechs (Exhibit 5).⁸ While there is potential for significant innovation from biotechs, there is an open question around whether sufficient absorptive capacity exists in the system to bring these programs through development. Indeed, our observations on the pharmaceutical industry suggest that manufacturers vary broadly in their abilities to identify, acquire, and gain from external innovation.

⁷ Pharmaprojects.
⁸ Ibid.

Vaccine candidates receive fewer ‘shots on goal’ relative to other biologics.

Attrition rate of programs, % from 2007–17



Examples of discontinued programs

■ Genocera Biosciences stops GEN-004, a universal-pneumococcal-vaccine program, because of low efficacy at Phase IIa

■ National Institute of Allergy and Infectious Diseases discontinues HIV-vaccine candidate after HVTN 505 trial (Phase IIb) because of no efficacy

■ Aeras discontinues MVA85A, a tuberculosis-vaccine candidate, because of low efficacy at Phase II/III

■ GlaxoSmithKline stops Simplirix, a genital-herpes-vaccine candidate, after Phase III failure because of no efficacy with herpes simplex virus (HSV) type 2 (HSV-2), only with HSV-1

Note: “Shots on goal” = fewer vaccine candidates are advancing to clinical studies.

Source: Pharmaprojects, Pharma Intelligence by Informa, September 2018, pharmaintelligence.informa.com; McKinsey analysis

The external market expects a return to growth, with analysts forecasting 6 to 9 percent growth in the global vaccine market over the next five years.⁹ In addition, there is considerable potential for new antigens as well as novel synthetic modalities (for example, messenger-RNA-based products). Inherent in these market assumptions are the successful Phase III completion of several vaccines in development as well as further advancements in innovation. The key question is whether the vaccine industry can overcome several challenges that are currently affecting innovation.

Challenges to innovation in vaccines

Our research on industry trends suggests

reinvigorating vaccine innovation will require addressing three underlying issues:

- increased investment requirements for mid- and late-stage R&D and manufacturing
- increased opportunity cost as relative investment economics converge with other biologics
- higher technical complexity and commercial uncertainty compared with recent innovations

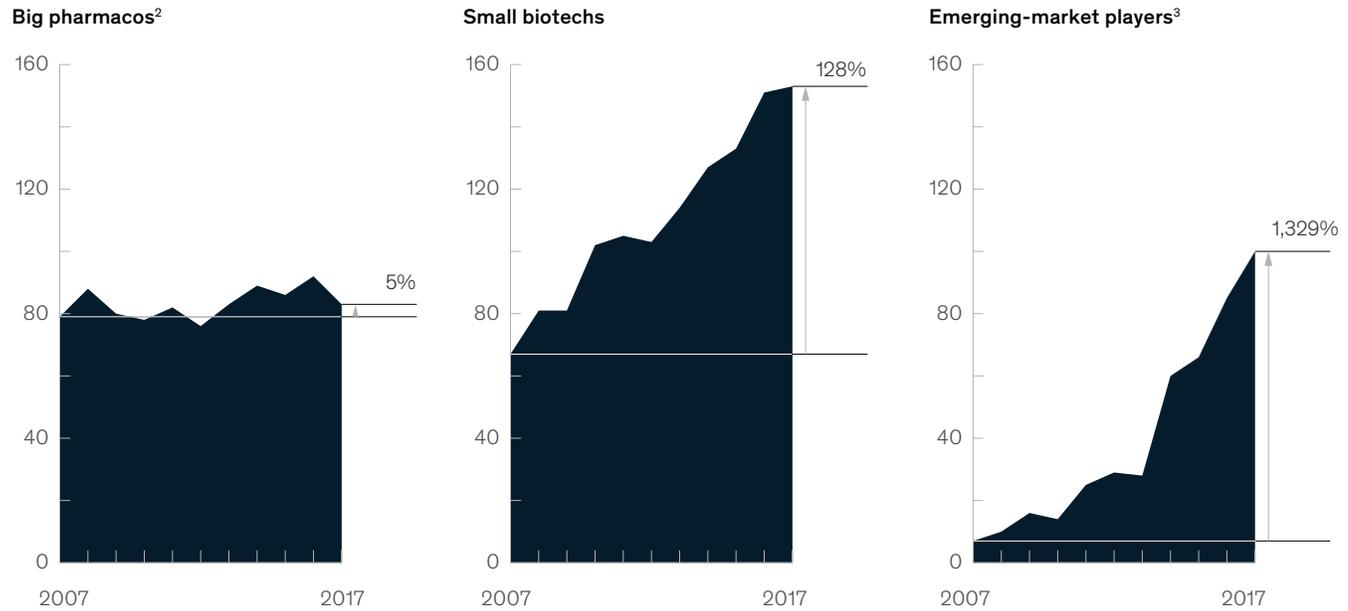
These challenges have the potential to affect different categories of vaccine manufacturers in different ways. On one side, they could create opportunities for innovation by new players. On the

⁹ EvaluatePharma.

Exhibit 5

The market is starting to see an increase in the number of new vaccine programs, largely driven by small biotechs and emerging-market players.

Vaccine-development programs globally,¹ number of programs



¹ Includes only infectious-disease vaccines, both prophylactic and therapeutic; excludes all cancer vaccines.

² Refers to top 20 players with vaccine pipelines, including in-licensed products.

³ Including Japan.

Source: Pharmaprojects, Pharma Intelligence by Informa, September 2018, pharmaintelligence.informa.com; McKinsey analysis

other side, they may create structural barriers that offer an advantage to existing players.

Increased investment requirements for R&D and manufacturing

Emerging trends contributing to a progressively challenging environment for innovation are the increases in investment requirements for R&D and manufacturing. These shifts in the broader infrastructure affect the overall economic equation of the vaccine industry by increasing the length of time and the costs associated with innovation.

On the R&D side, regulatory scrutiny, overall, is on the rise across more complex products (for example, biologics, vaccines, and other sterile injectables),

with longer timelines for vaccine approval (Exhibit 6).¹⁰ Also, given the preventive nature of these drugs, vaccines face a heightened bar for quality and safety, which thereby adds both complexity and additional cost throughout the development process.

In addition, many of the pipeline programs have lower incidence rates than in prior vaccine innovations and thus face evolving clinical-trial requirements. Clinical trials need to elicit a strong and lasting immune response and require a natural incidence of the disease where the trial is being conducted. Developing a vaccine for diseases with a lower incidence requires many more participants and sites to demonstrate efficacy, increasing both the cost and the duration of the trials.

¹⁰Ibid.

On the manufacturing side, we have seen shortages, recalls, and other manufacturing challenges in recent years. Recent examples include recalls of typhoid and varicella vaccines because of efficacy concerns as well as shortages and prequalification removals for pediatric combination vaccines because of manufacturing-reliability issues. These issues have resulted in lost sales and significant investment requirements to transform vaccine-manufacturing networks.

Increased opportunity cost as relative investment economics converge with biologics

Increased technical challenges are resulting in the convergence of the success rate of bringing vaccines to market with that of bringing other biologics to market. However, given the higher revenues derived from blockbuster biologics compared with vaccines—for example, the largest

biologic’s revenue is more than two to three times greater than the largest vaccine’s revenue (pneumococcal conjugate vaccine had peak revenue of \$6 billion)¹¹—this convergence of success rates reduces the relative attractiveness for investment in vaccines compared with the past, especially as the largest global vaccine manufacturers all have competing priorities. As pharmaceutical companies allocate capital to opportunities with the highest returns on investment, this change in the relative investment economics will be a consideration in future decision making for vaccine innovation.

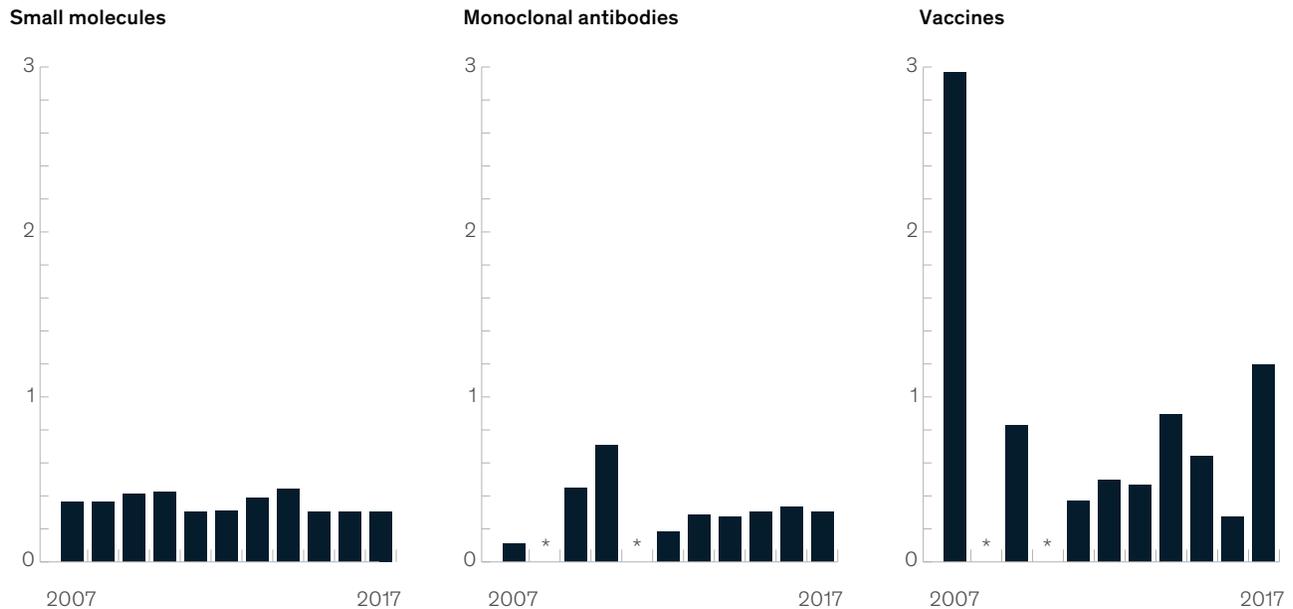
Higher technical complexity and commercial uncertainty compared with recent innovations

Many vaccine-industry leaders consider the recent major innovations (such as pneumococcus, rotavirus, and HPV vaccines) to be lower-hanging fruit in immunization—these vaccines had high

Exhibit 6

In the United States, the time to regulatory approval for vaccines is consistently longer than for other drug categories.

Median time to approval by drug technology,¹ thousands of days



¹Per US Food and Drug Administration; * indicates no approvals were recorded.
Source: EvaluatePharma, Evaluate, September 2018, evaluate.com; McKinsey analysis

¹¹ Ibid.

commercial potential and higher relative technical feasibility. The remaining potential innovations face increased commercial uncertainty and technical complexity in an environment of increasing R&D and manufacturing investments, as previously described.

From a commercial perspective, the pipeline of remaining innovations has a different profile (Exhibit 7)—the absolute size of relevant populations is smaller, and the programs have less established pathways compared with pediatric or adolescent vaccines, which have recommended immunization schedules. In this context, capturing the full market potential still requires navigating a complex vaccine care flow that has many influences and inputs (Exhibit 8). Obtaining the recommendation for inclusion in immunization schedules is the most uncertain step, as vaccine

manufacturers typically have limited visibility on what recommendations to expect. This step is critical to securing reimbursement and access to markets, so the situation builds additional uncertainty related to return on investment for vaccine manufacturers. Also, once a vaccine is on market, capturing market share requires navigating a broad set of stakeholders (physicians, retailers, payers, and patients), often with uncertain pricing and market demand contributing to additional commercial risk.

Regarding technical feasibility, the remaining pipeline innovations are challenging. In particular, potential blockbusters are often long-sought-after vaccines that have been tried (and failed) multiple times in the past (for example, HIV and universal flu vaccines).

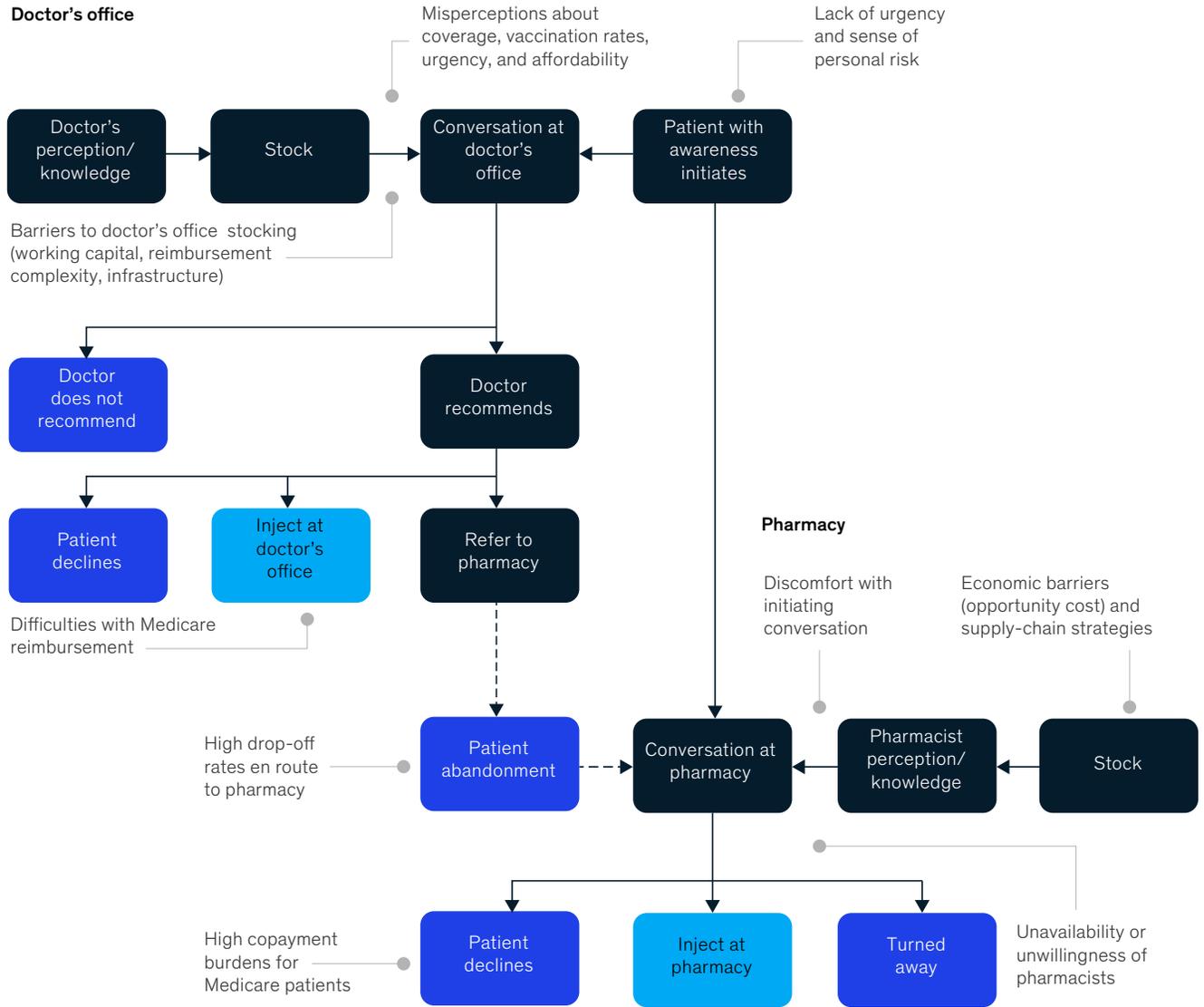
Exhibit 7

For challenging vaccine targets, it is important to assess commercial attractiveness and technical feasibility.

Assessment of commercial attractiveness	Assessment of technical feasibility	Example of challenging vaccine target
 <p>Volume Is a large population at risk? Does disease have high incidence?</p>	 <p>Natural immunity Does pathogen trigger antibody response and confer immunity after infection?</p>	HIV
 <p>Price Are people or payers willing to pay for vaccine? Are other vaccines or treatments available?</p>	 <p>Adaptability of pathogen Is there high antigenic variability, or does pathogen mutate/evolve quickly?</p>	Universal influenza
 <p>Ability to access market Are there existing commercial channels? If not, possible to make commercial access work?</p>	 <p>Strength of immune response Can adequate immune response be achieved? Are adjuvants necessary, and do they work?</p>	Pertussis
	 <p>Clinical trials How easy are clinical trials (ie, finding population at risk, diagnosing, prevalence of disease)? Is there correlate of protection?</p>	<i>Clostridium difficile</i>

Capturing share requires navigating a complex vaccine care flow with many influences and inputs.

Illustrative example of vaccine care flow and associated challenges



Stepping back, as the sources of growth shift from relatively low-hanging fruit to new opportunities for innovation, we see six vaccine archetypes emerging with varying levels of technical complexity and commercial opportunity (Exhibit 9):

1. **High-income markets.** Vaccines can target diseases in high-income markets, including healthcare-acquired infections (for instance, *Clostridium difficile* and staphylococcus infections), as well as other disease areas (for example, norovirus). These programs

have moderate technical feasibility but vary in commercial potential. For example, nosocomial-infection vaccines have high market potential but unclear commercial models and indications (for instance, they may not have clear immunization schedules), whereas other vaccines for high-income markets have moderate commercial potential and a mix of potential commercial models.

2. **Potential blockbusters.** Vaccines can target high-burden diseases with large global potential patient pools (such as HIV and respiratory syncytial virus) carry a high commercial potential. Pregnant women, for example, make up a population with significant unmet need remaining in immunization. Challenging technical complexity results in low to moderate technical feasibility for these innovations.
3. **Treatments.** Vaccines can be used as methods of treatment to fight existing diseases or conditions, rather than as preventative measures. Potential applications for these vaccines include oncology and smoking-cessation, as well as infectious-disease treatment. High unmet need results in a high commercial potential for these programs, but technical feasibility is low to moderate.
4. **Incremental improvements.** Improvements to existing vaccines can address unmet needs (for example, improvement in efficacy, duration of protection, and ease of use). While technical feasibility for these programs is moderate to high, the commercial value is uncertain, particularly in assessing the prices these incremental innovations can command.
5. **Emerging threats.** Vaccines can target emerging epidemiology threats and future priorities for innovation (for instance, Ebola virus and Chagas disease). These programs have an uncertain commercial demand profile, given the lack of clarity on the willingness of governments and agencies to stockpile significant amounts or pay more than “costs” to maintain supply options.

The technical feasibility is moderate and varies by disease.

6. **Low-income markets.** Vaccines can target diseases with higher burden in low-income markets (for example, tuberculosis and malaria) with moderate commercial potential and significant technical challenges. The evolution of supply and demand for vaccines in emerging markets creates significant ambiguity, compounded by the entrance of new local players. In addition, as Gavi countries (developing countries that receive support from the Gavi public–private partnership to increase access to vaccines) transition to take over responsibility for financing vaccine programs, growth in those emerging markets may slow—as experienced in Angola and the Republic of the Congo, where the governments have struggled to meet their cofinancing requirements in recent years.

Where do we go from here?

Given the commercial and technical challenges and the criticality of vaccines in advancing public health, continued innovation in the vaccine industry can best be supported via a comprehensive and shared agenda across key stakeholders: researchers, manufacturers, governments, policy makers, and payers. Several potential solutions might contribute to refueling the vaccine innovation engine.

Demand clarity

Earlier clarity on market demand would provide increased commercial certainty for vaccine manufacturers by helping to identify the priority innovations to address unmet market needs. One potential method might be to publish target-product profiles on the desired innovations. In addition, the profiles could include advance recommendations that would clarify likely recommendation or use given a specific profile, which would be particularly relevant for innovations in high-income-market, nosocomial-disease vaccines (archetype 1), as well as for innovations in treatment vaccines (archetype 3).

Six archetypes of vaccine innovation are emerging.

Archetype	Profile	Examples
High income + nosocomial  <ul style="list-style-type: none"> ● Vaccines targeting healthcare-acquired infections with larger burden in high-income markets 	<ul style="list-style-type: none"> ● Moderate technical feasibility ● Nosocomial: high market potential but unclear commercial model/indication ● Others: moderate commercial potential and mix of commercial models 	<ul style="list-style-type: none"> ● <i>Clostridium difficile</i> ● Staphylococcus ● Norovirus
Potential blockbusters  <ul style="list-style-type: none"> ● Vaccines targeting high-burden diseases with large potential patient pools 	<ul style="list-style-type: none"> ● High commercial potential—large burden of disease and large potential patient pools ● Low–moderate technical feasibility 	<ul style="list-style-type: none"> ● HIV ● Universal influenza ● Respiratory syncytial virus ● Hepatitis C
Treatments  <ul style="list-style-type: none"> ● Vaccines fighting existing diseases/ conditions rather than trying to prevent them 	<ul style="list-style-type: none"> ● High commercial potential ● Low–moderate technical feasibility 	<ul style="list-style-type: none"> ● Oncology ● Smoking cessation
Incremental improvements  <ul style="list-style-type: none"> ● Improvement to existing vaccines to address unmet needs (eg, efficacy, duration of protection, ease of use) 	<ul style="list-style-type: none"> ● Uncertain commercial potential, especially on price ● Moderate–high technical feasibility 	<ul style="list-style-type: none"> ● Seasonal influenza ● Pertussis ● Typhoid ● Measles
Emerging threats  <ul style="list-style-type: none"> ● Vaccines targeting emerging epidemiology threats and future priorities for innovation 	<ul style="list-style-type: none"> ● Uncertain commercial potential—unclear reliability and scale (eg, vaccine stockpiles) ● Moderate technical feasibility 	<ul style="list-style-type: none"> ● Ebola ● Zika ● Middle East respiratory syndrome
Low-income markets  <ul style="list-style-type: none"> ● Vaccines targeting diseases with higher burden in low-income markets 	<ul style="list-style-type: none"> ● Moderate commercial potential and mix of commercial models ● Low–moderate technical feasibility 	<ul style="list-style-type: none"> ● Malaria ● Tuberculosis

Value communication

Stakeholders could consider becoming more active in articulating priorities and value associated with material improvements to an existing standard of care (for example, addressing whether an improved

Haemophilus influenzae type B vaccine would achieve market premium and whether universal flu vaccines are adequately valued). This improved transparency would be particularly relevant for innovations addressing incremental improvements

in vaccines (archetype 4) as well as potential blockbusters (archetype 2).

Economic incentives

One potential approach to creating incentives for innovation is to facilitate funding for new models of industry partnership for both emerging threats (archetype 5) and low-income-market unmet needs (archetype 6). CEPI has made noteworthy progress in building alliances to finance and coordinate the development of new vaccines to prevent and contain infectious-disease epidemics. However, as CEPI primarily focuses on early-stage development (through Phase II clinical trials), additional solutions are still needed to address the challenge of funding the high-cost late-stage development.

Collaboration and data sharing

Improving transparency and data sharing could be valuable in overcoming technical challenges and achieving breakthroughs where they are most needed. Public-private partnerships may be particularly relevant for archetype-4 innovations, such as vaccines for HIV, tuberculosis, and malaria treatment. In such cases, significant need remains, but there are critical technical challenges, and the expected economics do not currently warrant industry leadership. A second form of collaboration could be to develop new technology platforms that enable shared production across antigens; this would be particularly valuable for emergency-

response innovations (archetype 5) to enable rapid scale-up. A third could be to generate more data around the burden of disease for pathogens that may be emerging or simply poorly understood. Finally, enhanced clarity on the public end-to-end vaccine and immunization agenda—from funding early research to trial design and preferred clinical-trial-site networks and, ultimately, to approval and market access—could boost innovation.

Early consultation on innovation design

Manufacturers could seek early and active engagement with regulatory and recommendation agencies throughout the development life cycle of new vaccines to obtain timely input to key decisions, including trial design. This could help to derisk the commercial uncertainty of innovation.

After a period of significant growth over the past two decades, vaccine innovation faces several challenges—namely, increased investment requirements for R&D and manufacturing, higher opportunity cost as relative economics converge with biologics, and greater technical complexity and commercial uncertainty compared with recent innovations—going forward. However, we believe there remains significant opportunity for vaccine manufacturers and other stakeholders (regulators, policy makers, and payers) to facilitate the next wave of vaccine innovation.

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