

FROM THE ANALYST'S COUCH

Infectious disease vaccines

Angela K. Shen and M. Timothy Cooke

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Vaccines have a huge impact on human health in both industrialized and developing countries, but account for a small fraction of biopharmaceutical industry sales. Just 3.5% (\$28 billion) of worldwide prescription drug sales were from vaccines in 2017, according to data from EvaluatePharma (FIG. 1; see Related links).

Given the impact of vaccination on public health, policy makers and other stakeholders support the development of new and improved vaccines and the optimal use of existing licensed vaccines. A recent report mandated by the US Congress summarizes the current vaccine development landscape (see Related links). This report concluded that much progress is being made in understanding the complex scientific issues for current and future vaccine targets and provided recommendations on supporting further vaccine development. It is clear that new innovative and flexible public–private partnerships will be essential to incentivize the development of vaccines through licensure when market incentives are not strong enough to pull development through to commercialization. Given this context, we explore three questions in this article: first, what is the status of the development pipeline for infectious disease vaccines; second, which types of companies are engaged in these programmes; and third, what are the implications for the future?

The vaccine pipeline

In October 2017, the Pharmaceutical Research and Manufacturers of America (PhRMA) published a pipeline of 144 infectious disease vaccines. This clinical-stage pipeline included vaccine candidates from companies in the US, Europe, Japan, Korea, Canada and Australia, but did not include candidates from developing country manufacturers that tend to spend less on R&D and focus on increasing access to vaccines through low-cost manufacturing (*Hum. Vaccin. Immunother.* **12**, 2469–2474; 2016). Using this list as a starting point for a review of company websites and ClinicalTrials.gov (see Related links), we verified 115 programmes as active and removed 29 for various reasons

(for example, the candidate was approved, the programme was terminated, the programme was inactive or no corporate sponsor was identified). An additional 17 candidates identified on company websites and cross-referenced on ClinicalTrials.gov were added, resulting in a final data set of 132 programmes (as of 28 February 2018). Of the 132 vaccine development programmes that target 46 different infectious diseases (see Supplementary Table 1), the four most common targets are influenza (16%; 21 candidates), HIV (12%; 16 candidates), respiratory syncytial virus (7%; 9 candidates) and Ebola virus (6%; 8 candidates).

To provide a rough estimate of the robustness of this vaccine pipeline, historical success rates can be applied across the pipeline overall. For vaccine candidates at phase I, the probability of becoming licensed has been reported as 22%, which increases to 30% for phase II candidates and 64% for phase III candidates (*Nat. Biotechnol.* **32**, 40–51; 2014). Applying these average success rates to the current vaccine pipeline gives some indication of the likelihood that a vaccine will ultimately be licensed from the pool of candidates. Of 24 pathogen targets

for which there is no licensed vaccine, there are only three — *Clostridium difficile*, Ebola virus and respiratory syncytial virus — for which a candidate has reached phase III development (TABLE 1), and the overall current pipeline for 19 of the targets would not be expected to yield a licensed vaccine based solely on the historical attrition rates (Supplementary Table 1).

Companies engaged in vaccine R&D

The vaccine market is highly concentrated, with just four companies — GlaxoSmithKline, Merck & Co., Pfizer and Sanofi Pasteur — accounting for about 90% of worldwide sales in dollars (FIG. 1a). Many of the other companies in the field involved in early-stage vaccine development rely on funding from multiple sources, including government agencies, non-governmental organizations and venture capital. However, the high costs of late-stage vaccine development, particularly those related to manufacturing, large clinical efficacy studies and commercialization, often prevent small biotechnology companies from pursuing further development. Instead, larger biotechnology or pharmaceutical

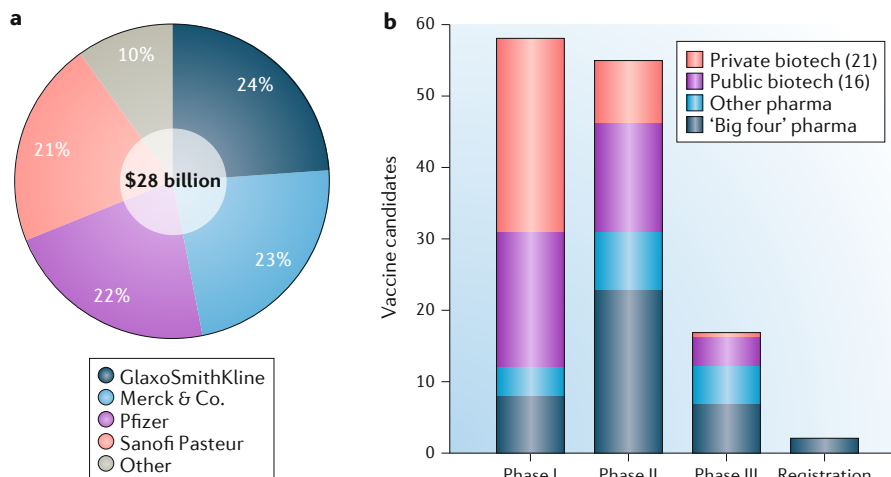


Fig. 1 | The commercial landscape and pipeline for infectious disease vaccines. a | Worldwide vaccine sales by value. The 'big four' pharmaceutical companies — GlaxoSmithKline, Merck & Co., Pfizer and Sanofi Pasteur — account for about 90% of the \$28 billion vaccine market as reported by EvaluatePharma, which is based on publicly traded companies. **b** | Infectious disease vaccine pipeline. The vaccine candidates were categorized by stage of development and type of company sponsor. Other pharmaceutical companies are CSL, Johnson & Johnson, Mitsubishi Tanabe Pharma and Takeda. The numbers of the other company types are indicated. See Supplementary Table 1 for further information.

Table 1 | Selected vaccine candidates in phase III development

Candidate	Sponsor	Target
PF-06425090	Pfizer	<i>Clostridium difficile</i>
TAK-003	Takeda	Dengue
DTP–IPV–Hib vaccine (Japan)	Sanofi Pasteur	DTP–IPV–Hib
MVA-BN Filo monovalent	Janssen/Bavarian Nordic	Ebola
Ad26.ZEBOV	Janssen	Ebola
V920	Merck & Co./NewLink Genetics	Ebola
Hepatitis A vaccine	PaxVax	Hepatitis A
Sci-B-Vac	VBI Vaccines	Hepatitis B
V212	Merck & Co.	Herpes zoster
H5N1 vaccine	Seqirus	Pandemic influenza
VLP QIV	Medicago	Seasonal influenza
Fluzone QIV HD	Sanofi Pasteur	Seasonal influenza
Seqirus QIV	Seqirus	Seasonal influenza
GSK209762	GlaxoSmithKline	Measles, mumps and rubella
Men Quad TT	Sanofi Pasteur	Meningococcal
RSV F protein vaccine	Novavax	RSV
Imvamune	Bavarian Nordic	Smallpox

Data are from 28 February 2018. HD, high-dose; QIV, quadrivalent vaccine; RSV, respiratory syncytial virus.

companies — with greater financial resources, existing capabilities and production facilities — shepherd vaccine candidates through phase III development and commercialization.

An analysis of the vaccine pipeline by clinical stage and by type of company provides an overview of these vaccine industry development dynamics (FIG. 1b). Most phase I studies (79%) are sponsored by public and private biotechnology companies. At phase II, this proportion decreases to 44% and to 29% at the phase III stage. For privately funded biotechnology companies, the proportion of candidates decreases from 47% at phase I to 16% at phase II and 6% at phase III. For phase II programmes and later, eight large pharmaceutical companies account for most of the development pipeline.

For private biotechnology companies, which contribute 44% of the phase I candidates, a key source of funding is venture capital or other private investment (Supplementary Fig. 1). A look back over 10 years of private investment in companies developing infectious disease vaccines shows a mixed story. Outside of two large funding rounds for PaxVax in 2015 and Moderna Therapeutics in 2016, the average annual investment in private companies developing infectious diseases vaccines was

\$57 million, which is modest considering that there are 21 private companies in this data set.

Multinational pharmaceutical companies are critical to maintaining or expanding the pipeline for infectious disease vaccines. The vaccine business units of these companies have to justify internal decisions about resource allocation between vaccines and all other therapeutic areas. Even among the ‘big four’ companies, vaccines comprise only 11–17% of their worldwide sales, making them important but not dominant products internally. The barriers to entry that have maintained these big four companies’ combined market share over decades include the large capital costs and highly specialized personnel required to build and operate vaccine manufacturing facilities. For preventive vaccines given to healthy people, the clinical trials can be large and very expensive. Combination vaccines against multiple pathogens, often used in paediatric vaccines to minimize injections, also create barriers to entry since they require access to multiple antigens. These are attractive reasons for the big four companies to remain in the vaccine business. New entrants can expect to invest a considerable amount of capital over a long period of time and this requires a long-term strategic commitment.

Outlook

To build a robust pipeline of vaccines across many infectious disease targets, a combination of novel science, private sector investment and public–private partnerships is required. Scientific breakthroughs could successfully tackle complex needs in vaccine design and immunology that have been challenging and illusive to date (for example, HIV vaccines). Molecularly defined nucleic acid-based vaccines have the potential to greatly reduce the cost-intensive and time-intensive chemistry, manufacturing and controls (CMC) required for the development of vaccines, although progress with DNA vaccines has been slower than anticipated and mRNA-based approaches still need to establish their utility in the clinic. However, government and non-profit organizations will need to continue to support companies, small and large, to ensure that infectious disease vaccine candidates live up to their potential as guardians of the public health.

Angela K. Shen¹ * and M. Timothy Cooke²

¹Angela K. Shen is a retired captain from the United States Public Health Service. This work was performed when she was at the National Vaccine Program Office, Office of the Assistant Secretary for Health, US Department of Health and Human Services, Washington, DC, USA.

²M. Timothy Cooke is at Ology Bioservices, Alachua Florida, USA and the National Vaccine Advisory Committee, Washington, DC, USA.

*e-mail: angela.k.shen@gmail.com

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Competing interests

M.T.C. is an employee and shareholder of Ology Bioservices, and a board member, consultant and shareholder of NovaDigm Therapeutics. A.K.S. declares no competing interests.

Disclaimer

The opinions expressed in this manuscript are those of the authors and not intended to represent the opinions of the National Vaccine Program Office and the National Vaccine Advisory Committee.

Supplementary information

Supplementary information is available for this paper at <https://doi.org/10.1038/d41573-018-00011-6>.

RELATED LINKS

ClinicalTrials.gov: <https://clinicaltrials.gov/>

EvaluatePharma world preview 2018, outlook to 2024:

<http://info.evaluategroup.com/rs/607-YGS-364/images/WP2018.pdf>

Encouraging vaccine innovation: promoting the development of vaccines that minimize the burden of infectious diseases in the 21st century: https://www.hhs.gov/sites/default/files/encouraging_vaccine_innovation_2018_final_report.pdf