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VIEWPOINTS

Premarket Development Times for Innovative Vaccines––To What Extent Are the Coronavirus Disease 2019 (COVID-19) Vaccines Outliers?

Reed F. Beall,[1,2] Aaron S. Kesselheim,[2] and Aidan Hollis[3]

[1]Department of Community Health Sciences, Cumming School of Medicine and O'Brien Institute of Public Health, University of Calgary, Calgary, Alberta, Canada, [2]Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; and [3]Department of Economics, University of Calgary, Calgary, Alberta, Canada

One reason expressed in surveys of people reporting coronavirus disease 2019 (COVID-19) vaccine hesitancy is how rapidly these vaccines have reached the market. To estimate the length of time the COVID-19 vaccine spent in research and development as compared to other novel vaccines, we apply previously established methods for estimating medical product development times, using the key associated patent filings cited by the manufacturer as the marker of when commercial development activity began. Applying these methods to a cohort of recently approved innovative vaccines and comparing them to the first-approved COVID-19 vaccine (BioNTech/Pfizer), we found key patent filings for the technology in this COVID-19 vaccine occurred 10.0 years prior to regulatory authorization. By this metric, the development timelines for innovative vaccines have been shortening since the 1980s, and the COVID-19 vaccine comfortably fits within this pattern. Vaccine development timelines have now even drawn to parity with many of the most commonly used drugs.

Keywords. vaccines; patents; vaccine development; COVID-19 vaccines; development time; vaccine hesitancy; BNT162b2; mRNA-1273; ChAdOx1-S.

A frequently mentioned reason for hesitancy surrounding the vaccines for coronavirus disease 2019 (COVID-19) is the perceived speed in which they were developed and approved for use [1]. In certain respects, the recent rapid development of COVID-19 vaccines has indeed been an unprecedented marvel in drug research and development. After the disease began receiving global press in January 2020, the genome of the virus was sequenced within the same month [2]. By April, more clinical trials related to COVID-19 had been launched than for other similar public health emergencies combined [3], including vaccine trials that would lead to regulatory authorizations starting 7 months later [4].

Past studies of drug development timelines have often used the date development activity began on the end product as the starting point, rather than the time from the discovery of the disease [5–7]. One marker of the beginning of this development activity that has been used in the literature is the key associated patent filing cited by the manufacturer. Patents protecting pharmaceuticals may pertain to the therapeutic substance itself; the formulation (eg, oral, injectable); the use in treatment for a specific medical condition; and a method of manufacturing. It is not uncommon for novel biotechnologies to find their ultimate therapeutic purposes at later stages in the development process prior to initiating clinical testing in humans. As such, a drug's earliest patents may not always include a reference to the specific treatment indication eventually listed on the label, either because its therapeutic utility was unknown at the time or it originally targeted different diseases. Since patent life is 20 years (with a possible extension for drugs of 5 years in the US), time-to-market from the earliest relevant patent has important commercial implications for manufacturers and is a marker of the length of development applied to the key technology or insight, regardless of the specific indication approved by a regulatory authority. Using this method, one recent study of all drugs approved by the US Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research between 2007 and 2016 found the median development timeline was 12.4 years (interquartile range [IQR], 9.7–15.3 years) [5]. This study did not include vaccines, which are approved by the Center for Biologics Evaluation and Research.

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Correspondence: R. F. Beall, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada (reed.beall@ucalgary.ca).

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Although other studies have examined time segments within the clinical testing and regulatory review timelines for cohorts of vaccines as compared to COVID-19 vaccines [8], we sought to evaluate the time from key patent filing related to a vaccine to marketing authorization. To determine the extent to which this COVID-19 vaccine is an outlier in terms of this measurement of development speed, we calculated premarket vaccine development timelines for a cohort of innovative vaccines in wide use and compared those development timelines to that of the COVID-19 vaccine BNT162b2 (generic name: tozinameran; manufacturer: BioNTech-Pfizer).

CALCULATING DEVELOPMENT TIMES OF INNOVATIVE VACCINES

We focused on a cohort of innovative vaccines flagged as novel and clinically important in Health Canada's "Register of Innovative Drugs," [9] a list that also includes vaccines and that has been maintained since 2006. Drugs and vaccines are included in the Register if the product contains a new active ingredient never before approved by Health Canada. We separated out vaccines as any products using the World Health Organization's (WHO's) Anatomical Therapeutic Chemical (ATC) codes for vaccines (ie, "J07…") [10]. This designation of "innovative" is important because noninnovative products can represent an improvement upon a previously approved product containing the same or a similar active ingredient. Development timelines for new versions of existing products may appear deceptively long (even though they are known to require less development time) when measuring from patent filings on the original product. For this reason, although some previously approved vaccine products that have been reformulated such that may qualify as a "innovative" according to Health Canada's definition, we have nevertheless used the originally approved version, rather than retaining both versions in our cohort. For example, we included Gardasil and Prevnar but not Gardasil 9 and Prevnar 13. We otherwise included in our cohort only products actively marketed in the United States and Canada to derive a sample of widely used products by manufacturers that have brought those vaccines to market in multiple countries with strong drug regulation infrastructures. Unfortunate delays in the development and premarket clinical testing of some vaccines for use in lower income settings have been documented, such as was observed in 2017 with an Ebola vaccine [11] and may therefore produce more heterogenous results with respect to speed-to-market.

To gather US regulatory approval dates as well as application submission dates, we consulted the FDA's database of approved vaccines [12] and the Database of Licensed Biological Products (Purple Book) [13]. To derive the keypatent filing date internationally for our cohort of innovative vaccines, we used the Espacenet database maintained by the European Patent Office to locate the priority filing dates globally for the American and Canadian patents associated with the products in our cohort [14]. This method for deriving the earliest patent filing date of a key patent associated with a medical product has been used in other published studies [5, 7]. As of 25 March 2021, regulatory bodies in the United States and Canada had not yet published patent information on the Pfizer-BioNTech COVID-19 vaccine; however, the inventors have disclosed in the scientific literature that they hold relevant patents, and other published reports identify these patent holdings [15, 16].

We calculated the development time for each vaccine by subtracting its regulatory approval date by the priority filing date internationally for the key patent related to the product in question. We report descriptive statistics, including the median and interquartile ranges as well as a time series analysis of development speeds based on the year of first patent filing.

We performed 3 additional analyses for sensitivity testing. First, we recalculated development time estimates based on the Health Canada authorization date to account for the possibility that development times may differ between countries and regulatory bodies. Second, we reran our calculations with the manufacturer's submission date of the application to the FDA, rather than the regulatory authorization date itself, to isolate the development time without the additional time required for regulatory review. Third, to assess whether the development speed for tozinameran is different from other COVID-19 vaccines, we repeated our process for calculating the development times for 2 other COVID-19 vaccines recently authorized by international authorities: the National Institutes of Health (NIH)-Moderna vaccine and the AstraZeneca/Oxford University vaccine.

VACCINE DEVELOPMENT TIMELINES

We found 422 products in Health Canada's Register of Innovative Medicines, of which 9 were vaccines. Three (Imvamune, Nimenrix, Synflorix) were excluded because they are not currently being marketed in the United States. Of the remaining 6 vaccines, 2 were newer versions of a preexisting product; the original versions of these products therefore were used in our final cohort. All 6 vaccines had key patents listed with both the US Patent and Trademark Office and Canadian patent sources. Indications for the vaccines included the prevention of pneumonia, meningitis, shingles, rotavirus, and genital cancers. There was a median of 15.3 years (IQR: 13.1–17.1 years) between the earliest patent filing internationally and FDA approval (Table 1).

The earliest key patent reported to be associated with the technology used to develop tozinameran had a filing date of 3 December 2010, 10.0 years prior to gaining FDA authorization. Using the same methods to calculate development times for other COVID-19 vaccines, we found similar results as compared to tozinameran. The full development time for the

Table 1. Cohort of Innovative Vaccines

Vaccine	Indication	Earliest Patent Filing	Date of Submission to FDA	Years to FDA Submission	Date of FDA Approval	Years to FDA Approval	Date of HC Approval	Years to HC Approval
Bexsero	To prevent invasive disease caused by *Neisseria meningitidis* serogroup B	1998–05–01	2014–07–24	16.2	2015–01–23	16.7	2013–12–06	15.6
Gardasil	To prevent genital warts and vulvar, vaginal, cervical, and anal cancers	1991–07–19	2005–12–07	14.4	2006–06–08	14.9	2006–07–10	15.0
Prevnar	To prevent *Streptococcus pneumoniae*	1981–08–31	1999–06–01	17.8	2000–02–17	18.5	2001–06–07	19.8
Rotateq	To prevent rotavirus gastro-enteritis	1987–11–30	2005–04–06	17.4	2006–02–03	18.2	2006–08–01	18.7
Shingrix	To prevent of herpes zoster (shingles)	2005–03–03	2016–10–21	11.6	2017–10–20	12.6	2017–10–13	12.6
Trumenba	To prevent invasive disease caused by *Neisseria meningitidis* serogroup B	2001–10–11	2014–06–16	12.7	2014–10–29	13.1	2017–10–05	16.0
Median (IQR) (n = 6)	-	…	-	*15.3* (IQR:13.1–17.1)	…	15.8 years (IQR: 13.5–17.8)	…	15.8 years (IQR: 15.1–18.0)
Tozinameran (BNT162b2)	To prevent severe COVID-19 disease	2010–12–03	2020–11–20	10.0	2020–12–11[a]	10.0[a]	2020–12–09	10.0
Median (IQR) (n = 7)	-	…	…	14.4 (IQR:12.2–16.8)	…	14.9 years (IQR: 12.8–17.5)	…	15.6 years (IQR: 13.8–17.3)

Abbreviations: COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; HC, Health Canada; IQR, interquartile range.
[a]The date used for this calculation is for emergency use authorization, not approval.

NIH-Moderna vaccine was 10.7 years [17] and the AstraZeneca/Oxford University vaccine was 9.8 years, using the date of emergency use authorization in Canada [18].

The full cohort of 7 vaccines reflect decreasing vaccine development times, ranging from 18.5 years for Prevnar (first patent filings in 1981) to 12.6 years for Shingrix, and finally to tozinameran (Figure 1).

When all development times were based on Health Canada (rather than FDA) authorization, the number of years was similar or slightly slower—a median of 15.8 years (IQR: 15.1–18.0, n = 6 drugs) without tozinameran and 15.6 years (IQR: 13.8–17.3, n = 7 drugs) with it (Table 1). When the date of submission to the FDA was used, the median development time for all 7 vaccines was 0.9 years shorter at 14.4 years (IQR:12.2–16.8 years, n = 7), as compared to 14.9 years (IQR: 12.8–17.5, n = 7) based on the FDA authorization date. Decreasing development times were still observed (Figure 1).

DISCUSSION

Although COVID-19 has only affected human beings for over a year, the technology underlying the tozinameran vaccine (as well as the COVID-19 vaccines by NIH-Moderna and AstraZeneca/Oxford University) had been in development for about 10 years before the vaccine first received marketing authorization. Development speeds for innovative vaccines have been steadily decreasing since the 1980s, and the COVID-19 vaccines fit within this pattern. These results demonstrating that the COVID-19 vaccines are comparable to previous vaccine development speeds may help alleviate some reluctance in vaccine-hesitant populations, and indeed, providing a fuller picture of the entire development timelines has been reported as providing reassurance [19].

Our results are consistent with remarks by US National Institute of Allergy and Infectious Diseases (NIAID) director Anthony Fauci, who estimated the development timelines for messenger RNA (mRNA) vaccines, based upon his own personal experience and knowledge of these products, to be about 10 years. He added that the basic science undergirding vaccine platform technologies pioneered by Barney Graham and other dates back a decade or more, were well established prior to the publication of COVID-19's genetic sequencing and were securely positioned to be effectively leveraged to address COVID-19 [19]. This speed is also on par with other innovative vaccines as well as novel drugs. In a previous study [5], the IQR of development spends for small-molecule and nonvaccine biologics was estimated as being between 9.7 and 15.3 years with 98 of those drugs with development times of ≤10 years. That study found no consistent trend of increasing or decreasing development speeds for those drugs over time. By contrast, in our cohort of innovative vaccines, we found a pattern of decreasing vaccine development times, culminating in tozinameran's 10-year development time.

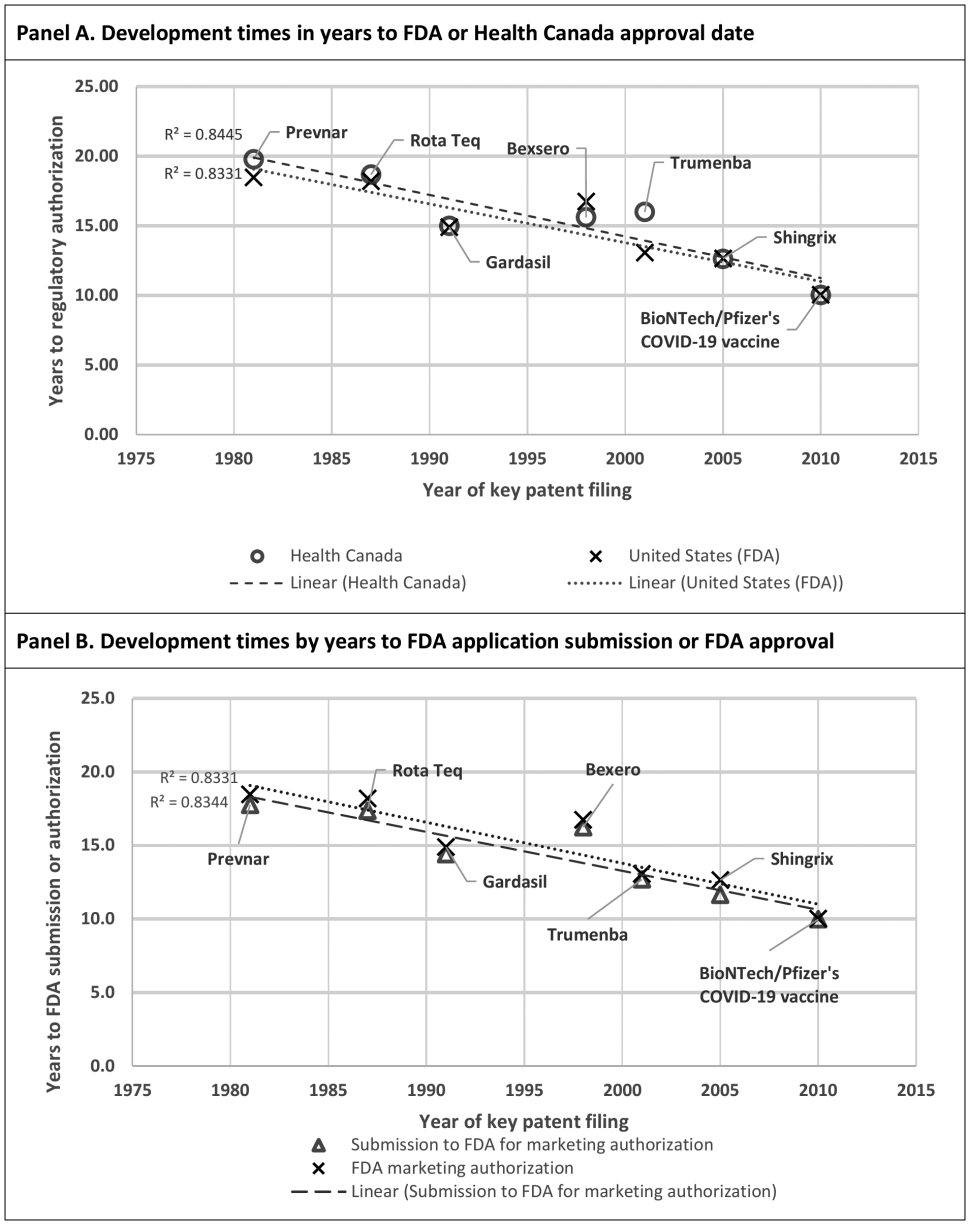

Figure 1. Time from first-filed patents to regulatory approval or submission. Innovative vaccine development times reflect a pattern of decreasing development times as defined as the number years from the earliest patent filing internationally and FDA approval date. This pattern held with a similar level of correlation when the Health Canada approval date or the submission date of the application for FDA approval was used rather the FDA approval date. Although the number of vaccines available for analysis is small, the R^2 values suggest a strong level of correlation at 0.83–0.84. Note that the date used for tozinameran is for FDA emergency use authorization, not approval. Abbreviation: FDA, Food and Drug Administration.

A limitation of our study is that although the inclusion criteria for our cohort of vaccines was highly selective and resulted in a sample of products relevant to the study at hand, it also resulted in a small sample specific to the needs of North American populations. Future study may expand the sample size to include more vaccines used in a wider variety of global settings to determine the extent to which the patterns observed by this investigation can be observed elsewhere. Second, while our identification of patents upon which to base our estimates of development times for the COVID-19 vaccines was corroborated by disclosures in academic publications of clinical trial results and by third-party patent landscape studies, this strategy differed from the one used for non-COVID vaccines that had key patent data available which had been disclosed to regulatory bodies by those manufacturers. Until these same patent data are publicly available for COVID-19 vaccines, we are unable to rule out the possibility that even earlier patents exist other than those located by our study or that those manufacturers would perceive other patents as "key" than the ones used for our study. Third, our study does

not capture the firsthand reports by tozinameran's inventors, who describe their design ideas coming into full formation within a single day [20, 21]. The importance of moments of scientific inspiration such as these cannot be understated and must be fully recognized. That said, the impressive patent record of these inventors (Ugur Sahin's name is on 140 patents and Özlem Türeci is on 40 as of March 2021) reflects an accumulation of innovation and capacity over time, which reached maturation at a moment when these scientists were positioned to mobilize the technology that they had been developing for many years to fight the novel coronavirus pandemic.

CONCLUSION

When considering speed-to-market of new medical products, it is important to consider the greater picture of when the key underlying technologies were originally developed for clinical use, rather than only considering the time between a disease's discovery and treatment's authorization to treat it. From this view, the COVID-19 vaccines' timelines are reasonably in line with previous experience of vaccine development and actually still required more time to develop than some of the most commonly used types of drugs today, including small-molecule drugs and non-vaccine-based biologics. This message may be reassuring for vaccine-hesitant populations who worry that the basic science undergirding the COVID-19 vaccines had been rushed.

Notes

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Data sharing. Study data analyzed in this manuscript is publicly available.

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