Strengthening Incentives for Vaccine Development

Michael Kremer

Christopher Snyder

Along with improvements in sanitation and nutrition, vaccines have been given credit for substantial reductions in mortality and morbidity. Yet an exhibit such as Figure 1 could raise concerns whether incentives to develop vaccines provided by public and private markets have kept pace with benefits derived from vaccines. The graph shows counts of new projects, captured by phase-3 clinical trials registered annually from 2006-2019 by the U.S National Institutes of Health (NIH). The number of vaccine trials (left scale), averaging about 75 per year for infectious diseases, is overshadowed by drug trials (right scale), averaging about 1,950 per year. Annual trials for infectious-disease vaccines trend sharply downward compared to the relatively constant number for drugs and cancer vaccines.

Vaccines Versus Drugs

A list of reasons could be offered for pharmaceutical manufacturers to prefer developing drugs to vaccines despite the high social returns from vaccines. Vaccines are part public good: increasing the number of people who are vaccinated reduces the infection risk for the unvaccinated, reducing their willingness to pay. A drug that treats symptoms but does not reduce transmission would not raise this free-rider problem and thus could be more lucrative. The free-rider problem associated with vaccines is well known and indeed has in part justified widespread government involvement in the vaccine market via programs such as Vaccines for Children in the United States. Such involvement may enhance incentives to develop and produce vaccines, but this is not guaranteed if negotiated prices end up being lower than what firms would charge on the private market. Other reasons for vaccines to be less lucrative than drugs could be that liquidity-constrained consumers may be better able to afford a sequence of payments for daily drug regimen than a large one-time payment for a vaccine delivering the same stream of health benefits. Behavioral economics might suggest that, owing to salience effects, willingness to pay

is higher for a drug taken while an illness is experienced than a vaccine preventing a yet-to-be-contracted illness.

Our foray into joint research on vaccines provided another reason why drugs may be more lucrative than vaccines: even positing that the *level* of demand is the same for vaccines and drugs, the *shape* of the demand curve may differ.[1] The shape of vaccine demand depends on the possibly quite skewed distribution of disease risk in the population. During the HIV epidemic in the United States, for example, a vaccine developer seeking to extract the high value concentrated in the high-risk population would find only a small market. Holding constant the average consumer value across drugs and vaccines, the distribution of values is different because disease-risk uncertainty is resolved once a person contracts the disease and becomes a customer for a cure. Of course, pharmaceuticals are not sold on pure private markets but mediated through insurance policies and government programs. Still, private-market outcomes bear on equilibrium presuming prices are negotiated in the shadow of private markets.

To quantify the potential size of this effect, Figure 2 draws the demand curve for a vaccine derived from a model of HIV risk that is linear in sexual partners reported in 2010 survey data. The inscribed rectangle shows maximum vaccine revenue, only about a quarter of the area under the demand curve, which one can show is the revenue generated by selling a drug to the expected number of consumers contracting the disease. Our previous mention of skewness in consumer values as leading to low vaccine profits was imprecise: a sufficient statistic for the vaccine-drug profit ratio is provided not by some moment of the risk distribution but by the distribution's resemblance to the worst case, the grey curve in Figure 2, a unit-elastic demand curve, arising from a Zipf distribution of risk (power law with exponent 1).[2]

Follow-on work moved from U.S. to international data to calibrate HIV pharmaceutical demand.[3] The distribution of income across countries is such that, for a range of estimates of the income elasticity of healthcare expenditures, the calibration for international drug demand looks as much like the Zipf worst case as the calibrated vaccine demand curve; both entailing weak incentives for pharmaceutical R&D. A variety of counterfactual exercises can be performed using the calibrated demands. For example, we show that uniform pricing would only deliver 44% of the profit earned from price discriminating across countries.

Quantifying the Free-Rider Problem

We mentioned that the free-rider problem associated with vaccines is well known. Less well known is which diseases present the worst free-rider problems and thus are key targets for subsidies. We investigate this question in work with Matthew Goodkin-Gold and Heidi Williams, taking the susceptible-infected-recovered (SIR) model, standard in epidemiology, and overlaying a vaccine market populated by rational consumers and profit-maximizing firms.[4]

We start by analyzing steady-state equilibrium for an endemic disease (such as HIV or measles) that requires every new cohort to be vaccinated. The key parameter is the index of disease infectiveness provided by the basic reproductive number, R_0 (the expected number of people directly contracting the disease from an infected person introduced into a susceptible population). While natural to think prevalence is increasing in R_0, in fact, prevalence is hump-shaped once economic incentives of consumers and producers are considered. For moderate values of R_0, the disease is too infectious to die out but not so infectious as to eliminate free riding. In our benchmark scenario, prevalence is maximized for $R_0 = 4$, falling into the range that epidemiologists have estimated for HIV, leading to some pessimism regarding the impact of an HIV vaccine absent government subsidy. But subsidies have shortcomings, too. The free-rider problem exacerbates monopoly incentives to distort quantity downward to keep prices high. We find that to counteract the severe distortions and achieve the first best when $R_0 = 4$ would require an outlandishly high per-unit subsidy, three times disease harm to a person. A more practical government policy would involve negotiating a bulk purchase for the population.

Adapting the analysis to the Covid-19 pandemic requires modifying the model to accommodate the possibility of a vaccine campaign to quell the epidemic before it becomes endemic. Despite mathematical complications, the nonmonotonicity of key variables (prevalence, optimal subsidy, etc.) in R_0 remains. We derive a simple condition on R_0 and the susceptible proportion of the population under which a vaccine exhibits increasing social returns. Policymakers have proposed rolling out limited vaccine supplies evenly across jurisdictions. Under the derived condition—satisfied for estimated Covid-19 parameters at the time of writing—vaccinating one jurisdiction at a time may be more efficient. For a disease with enough explosive potential, vaccinating a small group in two places may do little to slow its spread in either. To be sure, there are good reasons to spread *unlimited* supplies evenly—to everyone—and to vaccinate highly vulnerable or super-spreading individuals everywhere first. However,

increasing social returns provides a force in the opposite direction, toward concentrating limited supplies in fewer jurisdictions.

Advance Market Commitments

Vaccines are highly cost effective tools to improve global public health.[5] Yet the lag between the rollout of vaccines in rich and poor countries and the slow development of vaccines targeting diseases of poor countries suggests that private-market incentives to develop vaccines for poor countries may be particularly limited. Poor consumers cannot afford the high prices that would make a market lucrative. Aid agencies stepping in to purchase on behalf of the countries may use their bargaining power or public pressure to push down prices.

To enhance firms' incentives to supply vaccines to poor countries, Kremer and Glennerster proposed using a funding mechanism called an advance market commitment (AMC).[6] An AMC has donors set up a fund from which a subsidy is paid in exchange for the firms' promise to supply the vaccine at a price close to marginal cost even in the "tail period" after the AMC subsidy fund is exhausted. The donor's commitment to pay a subsidized price above cost protects firms' investments from hold up. The low price in the tail period mitigates market-power distortions. Since the purchase decision is ultimately made by client countries, the product must meet the market test, ensuring the program does not pay for products that satisfy the letter of contract terms (impossible to specify perfectly when set far in advance of production) but not user needs.

A pilot AMC directed by GAVI was announced in 2007 for a vaccine against pneumococcus, responsible for the death of over 700,000 children under five annually. The AMC targeted a second-generation vaccine covering strains endemic in developing countries. Much R&D had already been sunk in these vaccines, which were well into phase-3 trials; the pilot AMC was directed at incentivizing investment in capacity to satisfy the projected 200 million dose need in developing countries.

In work with Jonathan Levin, with whom we served on the Economics Expert Group tasked with finalizing design details for the pilot AMC, we explain the AMC idea, document the history of the pilot program, and provide a retrospective assessment of the program's ten-year run ending last year.[7] Figure 3 shows that coverage in GAVI countries converged to global levels

about five years faster for the pneumococcus vaccine than the rotavirus vaccine, also rolled out by GAVI and funded at levels similar to the AMC but structured in a different way.

Further work with Levin provides the first theoretical analysis of AMCs.[8] A key message is that AMC design depends on the technological distance of the product. We show that an AMC for technologically distant products like malaria vaccines may not work well to incentivize the capacity expansion needed for technologically close products like pneumococcus vaccines in the pilot. Firms can extract all AMC funds without the expense of expanding capacity; funds are extracted at a slower rate, but that just extends the subsidy period during which the fund accumulates interest. We show that a naïve AMC may be useless in incentivizing capacity. Incentives can be improved by adding a feature to the AMC called a supply commitment, limiting what firms can earn as a proportion of the target output they meet. (The pilot AMC added a supply-commitment feature on the recommendation of the Economics Expert Group.) Incentives can be further improved by structuring the AMC as an advance purchase commitment, a forcing contract that in effect takes the option of producing less than the target output away from firms.

Firms may have better private information about capacity and production costs for technologically closer products, posing an asymmetric-information problem for the AMC designer. Principles of mechanism design suggest that AMCs should allow firms to earn some information rent in the low-cost state of the world to avoid having to distort incentives in the high-cost state of the world further than necessary, but firm rents carry the political risk of being viewed as giveaways by those who ignore the asymmetric information problem. The asymmetric-information problem may be so severe with a technologically close product that an AMC could be cheaper for a technologically distant product despite having to defray R&D in addition to capacity.

AMC for a Covid-19 Vaccine

To avoid further illness and death during the Covid-19 pandemic, countries have gone into economic hibernation, resulting in near-term losses of $11 trillion and longer-term losses of $28 trillion in economic output alone.[9] A *New York Times* op-ed with Susan Athey and Alex Tabarrok called for an AMC to accelerate the development and distribution of a vaccine to shorten the pandemic and avoid even a fraction of these losses.[10] Spending billions to avoid

trillions of losses is an obvious economic calculation; less obvious are the unprecedented spending levels ($70 billion in the United States alone) and breadth of the program (capacity for 15 to 20 candidates installed at risk, before clinical trials are known to be successful) entailed.

Related formal research with Athey, Tabarrok, and the larger group of economists, epidemiologists, and policy experts in the Accelerating Health Technologies team[11] solves the optimal portfolio problem for a country selecting vaccines from the list of over 80 candidates in the pipeline at the outset of the pandemic.[12] We account for correlations patterns in success across candidates based on a hierarchical model of technology families and platforms parametrized with input from industry experts. The optimal portfolio, which may include some lower probability candidates that are less correlated with other technologies, is of course larger for richer countries with more GDP at stake, but even some of the poorest countries benefit from investing at risk in a handful of candidates. Shifting some funding from "pull" (paying for delivery of successful doses ex post, the standard way AMCs are structured) to "push" (paying developers' investment costs as they are expended) can reduce program costs since inducing the marginal candidate to enter with pull funding means paying a potentially large rent to inframarginal candidates with higher success probabilities. Push funding entails its own problems, providing weaker screening of candidates with unrealistic prospects (adverse selection) and disciplining of cost bloat (moral hazard);[13] so a mix of push and pull may be best and indeed was the strategy employed in the COVAX funding program launched by GAVI and Operation Warp Speed launched by the U.S. government.

---

[1] "Preventives Versus Treatments," Kremer M, Snyder, CM. NBER Working Paper No. 21012, March 2015, and *Quarterly Journal of Economics*, 130(3), August 2015, pp. 1167–1239.

[2] The distortions in pharmaceutical markets when consumer values have a Zipf distribution carries over to general product markets, as we show in "Worst-Case Bounds on R&D and Pricing Distortions: Theory with an Application Assuming Consumer Values Follow the World Income Distribution," Kremer M, Snyder CM, NBER Working Paper No. 25119, October 2018.

[3] "Preventives versus Treatments Redux: Tighter Bounds on Distortions in Innovation Incentives with an Application to the Global Demand for HIV Pharmaceuticals," Kremer M, Snyder CM. NBER Working Paper No. 24206, January 2018, and *Review of Industrial Organization*, 53(1), August 2018, pp. 235–273.

[4] "Optimal Vaccine Subsidies for Endemic and Epidemic Diseases," Goodkin-Gold M, Kremer M, Snyder CM, Williams H. NBER Working Paper No. 28085, November 2020.

[5] "Cost-Effectiveness and Economic Benefits of Vaccines in Low- and Middle-Income Countries: A Systematic Review," Ozawa S, Mirelman A, Stack ML, Walker DG, Levine OS. *Vaccine* 31(1), December 2012, 96–108.

[6] *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*, Kremer M, Glennerster R. Princeton, NJ: Princeton University Press, 2004. Additional work by Kremer on AMCs includes "Creating Markets for New Vaccines. Part I: Rationale," Kremer M. NBER Working Paper No. 7716, May 2000, and *Innovation Policy and the Economy* 1, pp. 35–72, "Creating Markets for New Vaccines. Part II: Design Issues," Kremer M. NBER Working Paper No. 7717, May 2000, and *Innovation Policy and the Economy* 1, pp. 73–118, and "Incentivizing Innovation: Adding to the Tool Kit," Kremer M, Williams H. *Innovation Policy and the Economy* 10, pp. 1–17.

[7] "Advance Market Commitments: Insights from Theory and Experience," Kremer M, Levin J, Snyder CM. NBER Working Paper No. 26675, February 2020, and *American Economic Association Papers and Proceedings*, 110, 2020, pp. 269–273. An early assessment of the AMC was provided by "Economic Perspectives on the Advance Market Commitment for Pneumococcal Vaccines," Snyder CM, Begor W, Berndt E. *Health Affairs* 30(8), August 2011, pp. 1508–1517.

[8] "Designing Advance Market Commitments for New Vaccines," Kremer M, Levin J, Snyder CM. NBER Working Paper No. XXXXX, December 2020.

[9] "A Long, Uneven and Uncertain Ascent," Gopinath G. *IMFBlog* October 13, 2020, https://blogs.imf.org/2020/10/13/a-long-uneven-and-uncertain-ascent/.

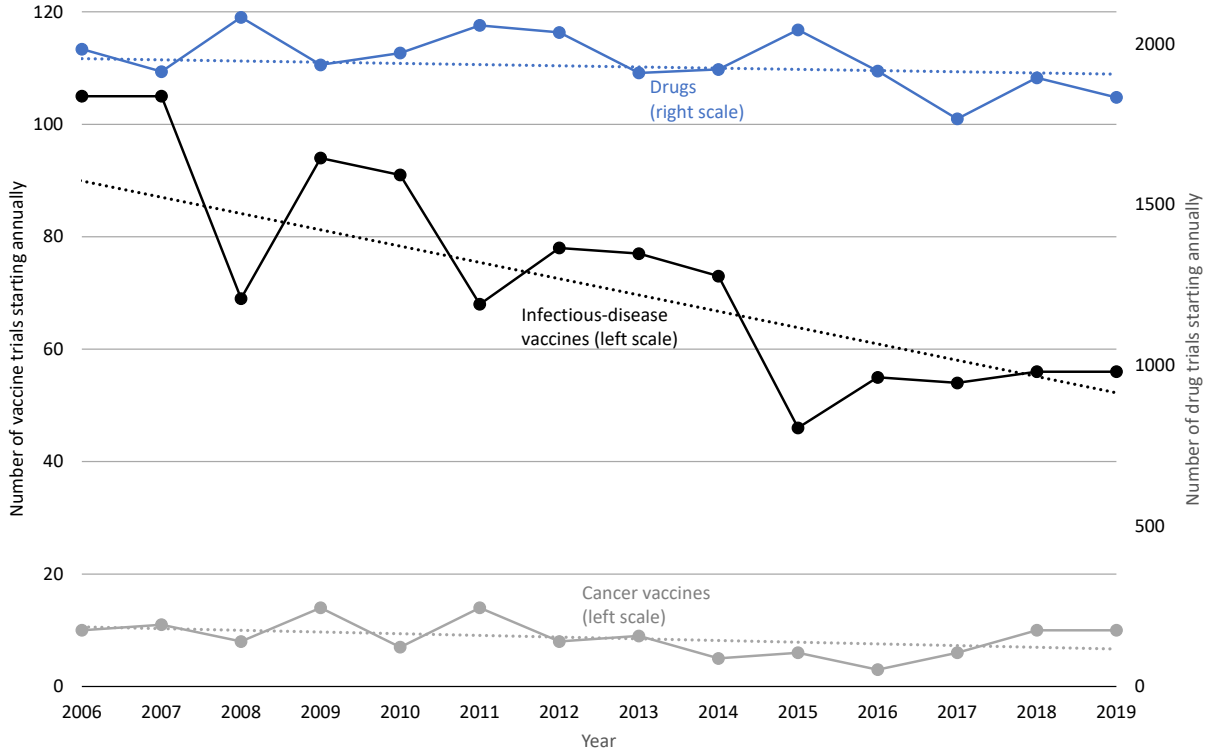
[10] In the Race for a Coronavirus Vaccine, We Must Go Big; Really, Really Big," Athey S, Kremer M, Snyder CM, Tabarrok A. *New York Times*, May 4, 2020, https://www.nytimes.com /2020/05/04/opinion/coronavirus-vaccine.html.

[11] For a complete list of participating team members, synopsis of our work, and other materials, see the website https://www.acceleratinght.org/home.

[12] "Investing in Accelerating a COVID-19 Vaccine," Ahuja A, Athey S, Baker A, Budish E, Castillo JC, Glennerster R, Kominers SD, Kremer M, Lee J, Prendergast C, Snyder CM, Tabarrok A, Tan BJ, Wiecek W. *American Economic Association Papers and Proceedings*, forthcoming, 2021.

[13] On the optimal design of a pure pull-funding mechanism, see "Designing Pull Funding for a COVID-19 Vaccine," Snyder CM, Hoyt K, Gouglas D, Johnston T, Robinson J. *Health Affairs*, 39(9), September 2020, pp. 1633–1642.

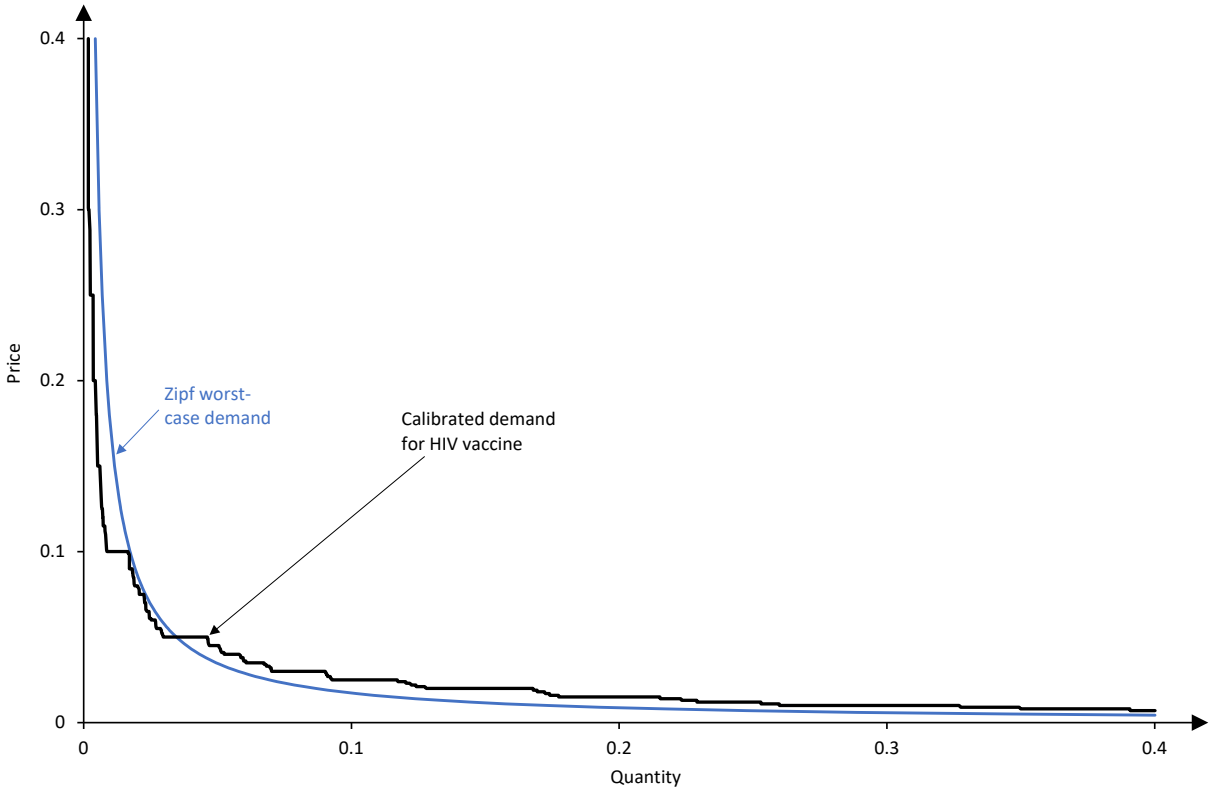
Figure 1: Count of Phase-3 Trials Initiated Annually by Product Type



Count of phase-3 clinical trials by product type registered on the U.S. National Institutes of Health and Library of Medicine's clinical-trial database between January 1 and December 31 each year over 2006-2019. Duplicates removed in counts. Linear trendlines drawn as dotted lines. The authors thank Nishi Jain for research assistance in preparing this figure.

Source: Authors' analysis of U.S. National Institutes of Health and Library of Medicine's clinical-trial database. [Internet.] Database from https://www.clinicaltrials.gove/ct2/home scraped on November 26, 2020.

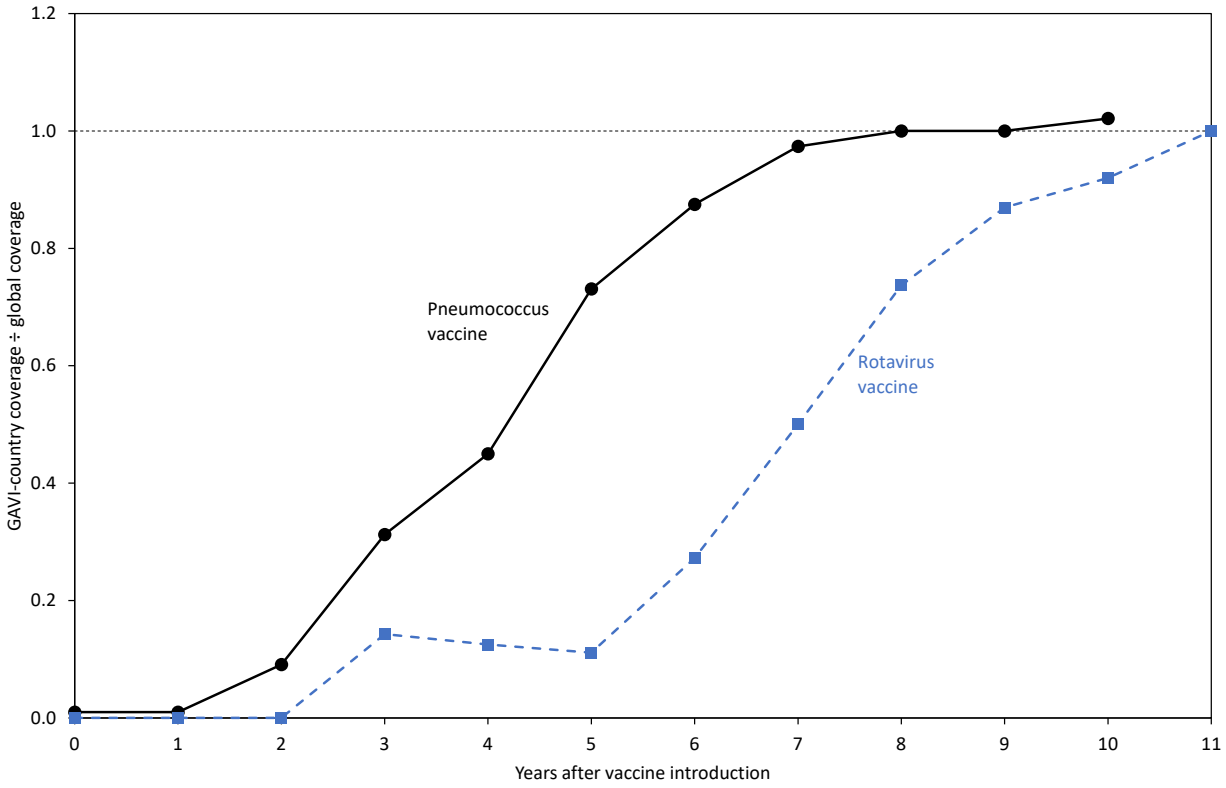
Figure 2: Inverse Demand Curve for Calibration with Infection Risk Linear in Number of Sexual Partners



Black curve is inverse demand calibrated by authors assuming that the only source of consumer heterogeneity is infection risk, which is modeled as linear in the lifetime number of sexual partners reported in the 2010 National Health and Nutrition Examinationl Survey (NHANES). Blue curve is the Zipf inverse demand curve attaining the theoretical lower bound on profit for given mean disease risk.

Source: Figure 6 of "Preventives Versus Treatments," Kremer M, Snyder C. Quarterly Journal of Economics 130(3), August 2015, pp. 1167-1239.

Figure 3: Coverage of Vaccines Rolled out by GAVI with and without an AMC



Plots of vaccine coverage in 73 GAVI-eligible countries divided by global coverage. Coverage defined as percentage of children receiving final scheduled dose (three for pneumococcus, two or three for rotavirus depending on schedule) by the nationally recommended age. Each series begins the first year the relevant vaccine was introduced globally: 2008 for pneumococcus and 2006 for rotavirus.

Source: Author calculations using WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) provided on the "Aggregate estimates" worksheet of the coverage_estimates_series.xlsx file downloaded December 18, 2019 from http://www.who.int/immunization/monitoring_surveillance/data/en/.