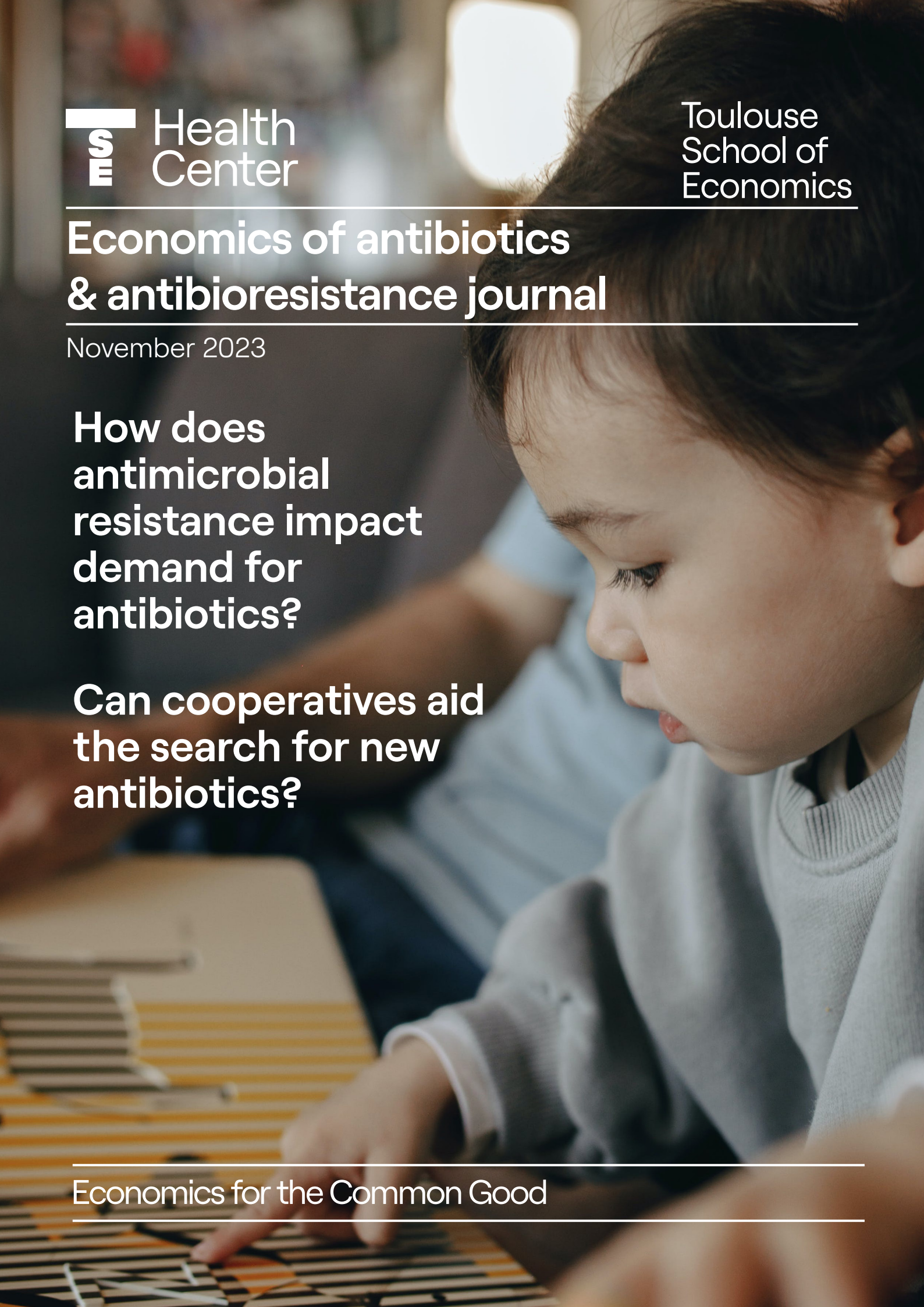

Health Center

Toulouse School of Economics

Economics of antibiotics & antibioresistance journal

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How does antimicrobial resistance impact demand for antibiotics?

Can cooperatives aid the search for new antibiotics?

Economics for the Common Good

Antibiotics for the Common Good

Antibiotics once stood as a beacon of hope, a panacea against a multitude of bacterial infections. They have revolutionized healthcare, extended lifespans and reduced the suffering caused by once-deadly diseases. However, these weapons are losing their edge as indiscriminate use of antibiotics accelerates the emergence of drug-resistant superbugs. The World Health Organization now describes antimicrobial resistance (AMR) as one of the biggest threats to global health, food security, and development. If left unchecked, estimates suggest it could cause up to 10 million deaths per year by 2050.

Governments must act boldly, but the fight against climate change has been a painful reminder that international agreements are often undermined by free riders and short-term thinking. Fortunately, TSE economists have shown that they can provide policymakers with the tools to align individual incentives with the long-term collective interest.

Launched with the support of the French government in 2021, the €17m ARPEGE project is an ambitious initiative that combines TSE expertise in a multisectoral approach to tackling AMR. Conducted jointly with Hospices Civils de Lyon, bioMérieux and Antabio the consortium has been tasked with expanding the arsenal of effective antibiotics, developing targeted diagnostics, and reducing bacterial transmission in hospitals. To enhance the value of such innovations, TSE Health Center will harness the power of cutting-edge economic techniques.

Governments must act fast, but joined-up thinking and judicious use of limited resources will also be essential. To face the AMR challenge, TSE economists are committed to providing informed solutions and rigorous evaluation of the effectiveness of public policies. In this journal, we highlight some of the latest investigations conducted by our researchers, including Nobel laureate Jean Tirole and TSE Health Center Director Pierre Dubois. Their analysis highlights the collective mechanisms that can ensure that all countries, businesses and global citizens embrace the need to change the way we use antibiotics.

We look forward to sharing more of their vital research in the future and thank all our partners and readers for their invaluable support.

About the ARPEGE project

ARPEGE is the french acronym for economic, diagnostic and therapeutic approach to antibiotic resistance. This pioneering project combines preventive, diagnostic, therapeutic and economic approaches, thus aiming to provide a multidisciplinary solution to the problem of antibiotic resistance. It is of major importance for public health, structuring innovation capacities and strengthening health systems through an innovative model.

How does antimicrobial resistance impact demand for antibiotics?

As governments scramble to fight the rise of antimicrobial resistance (AMR), it is vital to guide their efforts with careful analysis of the complex interactions of health policies such as antibiotic bans, limits and information campaigns. In a new study, TSE researchers Pierre Dubois and Gokçe Gokkoca evaluate the effectiveness of recent French initiatives by studying the impact of AMR on physicians' treatment decisions and the demand for antibiotic drugs. They also show how policymakers can get the best value for rapid bacterial detection and antibiotic susceptibility testing.

Gokçe Gokkoca
PhD student at TSE

Pierre Dubois
Professor of Economics at TSE

Why does antibiotic resistance pose such a serious threat to modern medicine?

If infections become untreatable with antibiotics, we can expect huge increases in hospital stays, surgery risks, medical costs and mortality. Recent estimates attribute 1.27 million deaths to bacterial AMR in 2019 worldwide. There are two reasons for the gravity of the situation. First, there are negative consumption externalities. The higher antibiotic use is, the faster resistance develops. This effect is also present in antimicrobial usage in livestock production and agriculture, exacerbating the problem. Second, there has been a steady decrease in the number of new antibiotics that are being developed and approved.

How are governments responding? And how can economists help?

There is consensus that additional incentives for innovation against AMR are needed, and various incentive policies for different stages of the research and development of antibiotics have been proposed (see TSE research by Dubois et al., 2022 and Majewska, 2022). But even if new medicines are developed, AMR will remain a major threat unless the world changes the way it uses antibiotics.

It is vital to preserve the current effectiveness of today's antibiotics by limiting their consumption. Action plans from health authorities worldwide recognize this issue and are intended to slow the development of resistance by limiting externalities through antibiotic stewardship programs. Most experts advocate a 'One Health approach', acknowledging the links between actions regarding humans, animals, agriculture, and the environment.

We need to understand to what extent physicians consider bacterial resistance in their decisions. Economists can then assess the effectiveness of policies intended to provide richer information on resistance, or that limit the use of antibiotics.

France has been struggling with high resistance rates, veterinary use and human consumption levels. In the past decade, this has prompted two consecutive campaigns to encourage antibiotic use only in necessary cases. The first met the goal of reducing antimicrobial use by 25%. The second set a goal of reducing use in specific classes such as fluoroquinolones, which are crucial resources for human medicine. France has also begun to offer financial rewards to physicians who issue fewer antibiotic prescriptions, especially for broad-spectrum antibiotics that target many types of bacteria.

To evaluate and improve such programs, we need to understand to what extent physicians consider bacterial resistance in their treatment decisions. Economists can then assess the effectiveness of policies intended to provide richer information on resistance, or that limit the use of certain antibiotics.

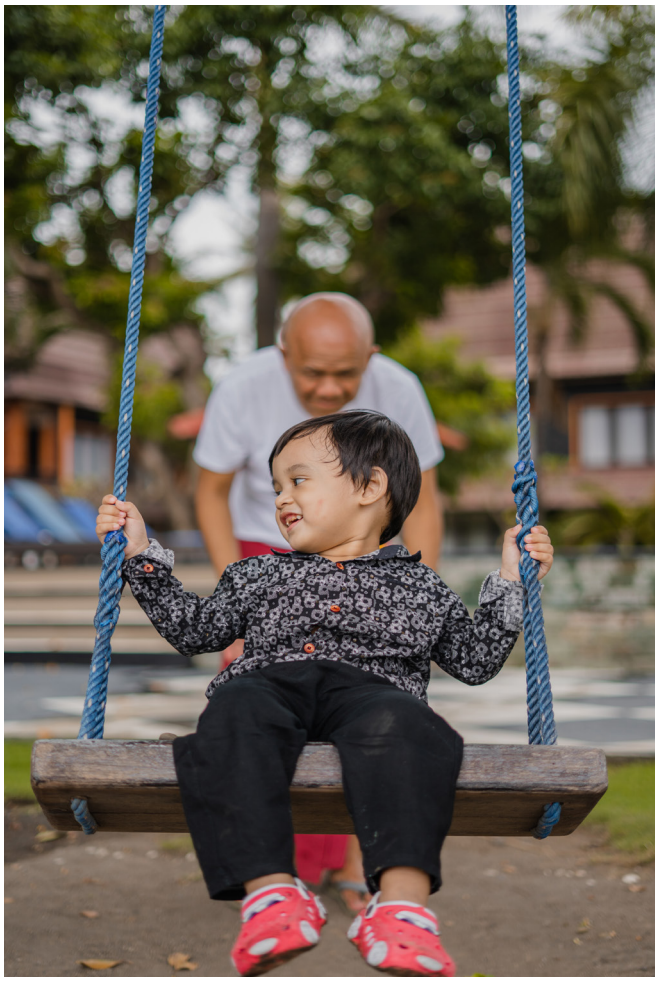
How does your paper study how physicians respond to antibiotic resistance when treating infections?

We employ multiple data sources to study the role of AMR on changes in prescriptions of antibiotics for treating cystitis (bladder inflammation). We use a representative sample of general practitioners in France between 2002 and 2019, which is a period long enough to observe meaningful variation in resistance. We focus on this specific infection because it is one of the most common reasons for antibiotic prescription, and is in most cases caused by E. coli bacteria which is becoming increasingly resistant to many drugs. This allows us to abstract from the physician's expectation about which bacteria caused the disease and to directly use the resistance of E. coli to identify the impact.

Our information model allows us to test whether physicians act on their expectation of current resistance levels, updating last year's resistance with the subsequent antibiotic consumption of humans and animals; or if they use only the resistance level from the previous year.

Estimating demand, we control for the endogeneity of prices and advertising. We also avoid a potential simultaneity problem between demand and resistance by exploiting the substantial variation in antibiotics sales for animals generated by French AMR campaigns and regulations. We then perform counterfactual analysis assessing the impact of decreasing veterinary use of antibiotics and limiting fluoroquinolone use to treat cystitis.

Rapid bacterial detection or antibiotic susceptibility testing are key tools in combating AMR. We provide a framework to analyze their added value in terms of savings per prescription and the change in treatment success probabilities.



What do your results suggest about the effectiveness of AMR policies?

Our results indicate that bacterial resistance affects prescription behavior, as physicians opt for antibiotics for which less resistance has developed. The degree of this substitution behavior varies by region. However, our information model does not provide evidence that physicians act based on expectation of resistance but only use last-year resistance, leading to potential mistakes that could be avoided with updated information.

Our counterfactuals analysis studies the effects of a ban on fluoroquinolones for the treatment of cystitis and limits on their use in animals. Both policies reduce resistance – by 1 percentage point and 4 percentage points, respectively – extending the life of the antimicrobial agent. These results can be regarded as a lower bound on the benefits of the policies, given that we do not account for the value of the long-term gains from lower AMR.

However, we also find that the two policies have opposing effects on substitution behavior and consumer welfare. In the case of the ban for humans, we observe substitution toward other valuable antibiotics that need to be saved for more complicated cases. In the case of limits on veterinary use, the policy impact is likely to be diminished by an increase in prescriptions for humans as resistance decreases.

How can your research help health authorities decide how to price diagnostic tests?

Rapid bacterial detection or antibiotic susceptibility testing with high accuracy are key tools in combating AMR. We provide a framework to analyze the added value of such diagnostic tests at the point of care in terms of savings per prescription and the change in treatment success probabilities.

For example, rapid bacterial detection allows physicians to make antibiotic prescription decisions with certainty rather than using empirical bacterial probability, reducing unnecessary prescriptions. Thus the higher the price of antibiotics and the lower the true rate of bacterial infection, the higher will be the value of the rapid bacterial detection test. The value of this test will be even larger if the more expensive antibiotics are the most used.

Unlike rapid bacterial detection, the antibiotic susceptibility test allows the physician to use patient-specific resistance information which improves the healing rate of patients. The value of this test thus also depends on the induced change in healing rate provided by this information: Mandatory testing is desirable if the value of the increased probability of being cured is greater than the combined cost of the susceptibility test and the antibiotic.

We can then provide a lower bound on the maximum price that would be optimal for an insurer to reimburse the test in a mandatory testing scheme. This maximum price depends on the probability of infection in society and the value of treatment for patients. It is a lower bound because we do not consider the additional long-term public health benefits of lower resistance. Future work could include these effects, as surveillance of bacterial resistance and data collection improves.

KEY TAKEAWAYS

- **Incorporating a wide range of factors that affect prescription decisions, this research reveals how physicians substitute to other antibiotics as AMR increases.**
- **Policies that rein in antibiotic use can reduce AMR. However, there may be unwanted side effects on the behavior of physicians and consumers, such as encouraging overuse of other valuable antibiotics.**
- **The mixed effects of such policies highlight the importance of a unifying approach that considers the entire ecosystem, such as the "One Health" approach adopted in France.**
- **Optimal pricing of rapid bacterial detection and antibiotic susceptibility testing depends on the probability of infection in society and the value of treatment.**

FURTHER READING

"Antibiotic Demand in the Presence of Antimicrobial Resistance" and other publications by these authors are available on the TSE website.
See also Dubois et al (2022) on "The Economics of Transferable Patent Extensions" and Majewska (2022) on "Incentivizing Novelty in Antibiotic Development".

Can cooperatives aid the search for new antibiotics?

Encouraging the spread of innovation will be crucial to tackling the health and climate challenges of the 21st century. Governments, private donors and multilateral organizations are eager to stimulate development of new medicines, infrastructure and green technologies, and joint procurement has become a popular strategy for both countries and businesses seeking to pool their purchasing power and reduce costs. Exploring the potential of cooperatives, a new paper by TSE researchers Paul-Henri Moisson, Pierre Dubois and Jean Tirole compares their performance with for-profit firms and analyzes desirable policy interventions in the corporate market

Paul-Henri Moisson
PhD student at TSE
Pierre Dubois
Professor of Economics at TSE
Jean Tirole
2014 Nobel Laureate in Economics & Honorary chairman of the J.-J. Laffont Foundation (TSE)

What inspires the formation of cooperatives?

Cooperatives may form when multiple users would benefit from a new technology or the production of a public good. Countries may work together to produce a new antibiotic, diagnostic or vaccine. Or to "re-shore" personal protective equipment, co-finance green R&D, or "learn-by-doing" with renewable energy. A consortium of car manufacturers may need a new infrastructure to build a battery for electric vehicles or a network of charging stations. A coalition of cities and builders may want to invest in a local green cement factory. Or a crowdfunding platform may seek to harness the interest of multiple investors.

The new antibiotic, technology or infrastructure may be provided by a for-profit, third-party supplier who has no in-house use for the technology and receives funding from the capital market. Alternatively, concerns about market power and access to innovation may trigger the creation of a cooperative of users. Cooperative members can allocate funding duties among themselves, assign usage rights, and split the cash-flow rights on the revenue from selling access to non-members, subsequent innovations or other derivative decisions.

What does your paper reveal about the obstacles faced by cooperatives?

We ask a simple question: In a world with no governance cost to forming a cooperative, should we expect cooperatives to be viable, and if so, to outcompete for-profit companies? One may conjecture that the higher social surplus created by the cooperative form gives it a decisive advantage. However, our theoretical analysis suggests that cooperatives are most likely to be outcompeted by for-profit companies.

Our main result is that in a "laissez-faire" context and if cooperatives cannot commit to exclude non-members from accessing the technology (for example, by committing not to sell a new vaccine to any country that did not participate in the investment), users' welfare remains the same whether or not cooperatives can compete in the corporate-form market. Indeed, the only way for a cooperative to emerge and not be preempted by a for-profit is to behave exactly like the latter. Therefore, from the perspective of users' welfare, the cooperative form is irrelevant -- unless governments or third-parties get involved.

"One may conjecture that the higher social surplus created by the cooperative form gives it a decisive advantage. However, our theoretical analysis suggests that cooperatives are most likely to be outcompeted by for-profit companies.

This result stems from free riding on the investment cost. Consider the case in which, once a cooperative has developed a new technology, it is in its interest to sell access to non-members. Then, potential members may prefer not to join the cooperative in the first place, thereby eluding their share of the investment cost, and to buy access to the technology once it has been developed by the cooperative. Hence, if the technology is financially viable, free riding constrains the cooperative's ability to secure funds and prevents it from developing the innovation before a for-profit. The incentive to preempt rivals leads to hasty investment and only a limited group of users gains access. If the technology is not financially viable, it will not be developed even when the investment cost is less than total willingness to pay. Public intervention is then needed to bring about investment.

In a few words, our intuition is that users can let others invest in the technology, then later purchase access. The cooperative's strength – a broader base of users – is also its weakness, as the extra users are reached through low prices that apply to late adopters, but also to the founders who always have the option to be holdouts. However, the cooperative may overcome its free-riding problem if it can deny future access to non-members: for example, by making extra production capacity exceedingly costly.

How does your model build on existing research?

The literature on cooperatives has stressed two obstacles to their formation: cash constraints for investors, and governance issues caused by conflicting objectives. These obstacles are absent in our model: Differences in willingness to pay is the only possible heterogeneity among our users. Once cooperative members have secured access to the technology, they all have the same objective of maximizing revenue (in the absence of externalities). This incentive alignment makes our irrelevance result surprising and powerful.

Our paper connects to the theory of clubs (Buchanan, 1965). When facing for-profit rivals, we show clubs of users can exist only if they can be exclusive, even though this is against their future interest. Our analysis is further related to studies on funding and governance of R&D. However, our paper introduces for-profits alongside cooperatives, and preemption concerns, and shows that they may make even costless and infinitely efficient crowdfunding irrelevant.

If investment costs are sufficiently low, the government should subsidize a cooperative to help it form and preempt for-profits. The policy question of when such interventions bring the most "bang for the buck" is crucial.

Our research is also linked to studies which suggest incomplete contracts can reduce incentives to free ride and that domestic politics may weaken international treaties. However, while these works focus on "non-excludable" common goods such as clean air or low carbon emissions, contributors in our setting can exclude others from the investment outcome that might be a new technology, antibiotic or infrastructure. All else equal, excludability limits free riding, which makes our irrelevance result all the more surprising.

How much confidence do you have in your results, given the complex impacts of antibiotics and other innovations?

We find that the irrelevance of cooperatives is a remarkably robust result that remains valid in the presence of externalities, whether they are borne solely by technology adopters, or by non-adopters as well. These externalities can be negative, such as when antibiotics generate resistance. Positive externalities can arise from green innovation, or diagnostics that allow healthcare systems to reduce antibiotic consumption and resistance, or vaccines to fight a pandemic. For competing entities, market externalities can be positive in the case of complementary products, or negative for substitutes.

In the health sector, drug prices often result from bargaining by governments in the interests of their users. Our result also holds in this context, as long as cooperatives do not have more bargaining power than for-profits. While government bargaining reduces the returns of a for-profit, it also reduces those of a cooperative and worsens its free-riding problem.

Cooperatives remain irrelevant when we allow technology developers to sell access at multiple dates. When we introduce rental or repeat purchases, the cooperative form becomes relevant only when the new technology is so profitable that a collusive oligopoly would be otherwise financially sustainable.

Should governments intervene in favor of cooperatives?

Our research suggests that benevolent, disinterested third parties may be key to improving access to innovation. These may be governments when users are private parties or regional authorities; or private donors and multilateral organizations when users are countries. To subsidize cooperatives, governments may offer "cheap" funding (below the going market rate); or restrict funding to cooperatives that are entirely owned by users. Unsurprisingly, we show that if investment costs are sufficiently low, the government should subsidize a cooperative to help it form and preempt for-profits.

The policy question of when such interventions bring the most "bang for the buck" is crucial, given the scale of global challenges such as antibiotic resistance and climate change. Our paper initiates the study of the marginal value of public funds in this context but much more work is needed to make the analysis operational.

To go further, we need to recognize that the regulator may have less information than the industry about demand or investment costs. The regulator may infer that the market is neglected from the absence of entry. Some information could be obtained through a market test, using investors' or users' willingness to co-finance the infrastructure. Such market tests may help governments to avoid investing in "white elephants", or not to invest more than necessary to stimulate desirable innovation.

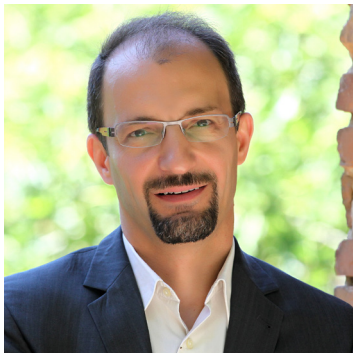
KEY TAKEAWAYS

- **Cooperatives are undermined by free riding, which reduces their ability to secure funding.**
- **Governments, private donors and multilateral organizations that act as impartial third parties can help cooperatives to develop new antibiotics and broaden access to innovation.**
- **Without this help, cooperatives will be outperformed by for-profits in financially viable markets, and unable to supply neglected markets.**
- **Further research on the effective use of public subsidies or regulation for cooperatives will be essential to address global challenges such as antimicrobial resistance.**

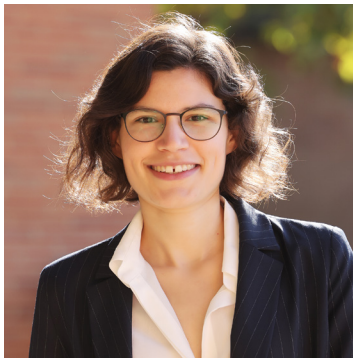
FURTHER READING

"The (Ir)Relevance of the Cooperative Form" and other publications by these authors are available to read on the TSE website.

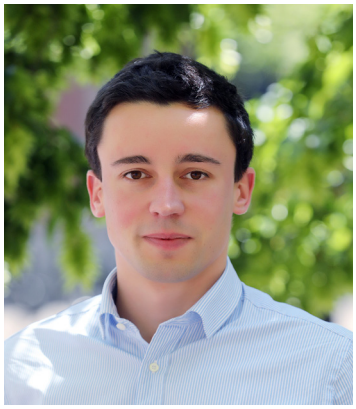
About the authors



Pierre Dubois *is Professor of Economics at TSE, fellow of the CEPR and of the Institute for Fiscal Studies in London, senior member of Institut Universitaire de France and Director of TSE Health Center. He is currently co-editor of the Journal of the European Economic Association. His work includes research on industrial organization, health and pharmaceuticals, food demand and applied econometrics.*



Gökçe Gökkoca *is a PhD student at TSE. Her research interests are empirical industrial organization, microeconometrics, and health economics. In particular, she is interested in understanding the specificities of the antibiotics market, their effect on physician behavior, and public policies targeting antimicrobial resistance.*



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He is laureate of numerous international distinctions, including the 2007 CNRS gold medal and the 2014 Sveriges Riksbank prize in economic sciences in memory of Alfred Nobel.

His research covers industrial organization, regulation, finance, macroeconomics and banking, as well as psychology-based economics. His work in health economics today focuses on the source of market failures for the innovation in antibiotics as well as the regulation and ethics of digital technologies in health care.

TSE expertise in the field of health economics

The Toulouse School of Economics (TSE) aims to undertake research that helps organizations in both the public and the private sector to address health issues and improve quality and access to care both in France and worldwide. For more than a decade, TSE economists have been studying such diverse topics as healthcare, innovation, ageing, pharmaceutical regulation, food and nutrition issues. The set of questions and problems for economists is huge. Researchers in economics can develop and use new tools to address questions of regulation and organization of healthcare and innovation.

In 2021, TSE expanded its footprint in this area by creating a Health Center aiming at developing research of excellence in the field of health economics. Combining TSE's own expertise with its private and public partners' financial support and knowledge, TSE Health Center supports a variety of research work in the field of health economics.

Research focuses

- Pharmaceutical industry and regulation
- Innovation in health
- Public healthcare, long term care and aging
- Food and healthy behavior economics
- Economics of pandemics

TSE Health Center gather more than 30 researchers from various background. TSE researchers are at the origin of many scientific publications, particularly in the field of antibiotic economics.

Our partners contribute to the scientific activities of TSE Health Center. Their support is essential to help TSE Health Center become one of the best research centers focused on health economics.

Find out more: www.tse-fr.eu/health

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