

Preventing the Spread of Antibiotic Resistance

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In 2018 in the US, about 3 million people got an antibiotic resistant infection and 50,000 died as a results (Center for Disease Control (2019)). Worldwide the situation is even more problematic with an annual estimated toll of 700,000 deaths. This figure is raising fast and the prediction is that in 30 years, those deaths may surpass mortality due to cancer (Tagliabue and Rappuoli (2018)). The Center for Disease Control estimates the annual cost for the US to be around \$ 55 billion (CDC (2011)). Resistance is a natural phenomena but has become one of the most alarming health issues. The main cause is due to the overuse and misuse of antibiotics. Those drugs are used to treat human infections, but their main use is in fact in animal production, mainly as a growth promoter, absorbing about 80 percent of the total production. Public policies have tried to convince the medical profession to prescribe antibiotics less and has also regulated the use of antibiotics in livestock in European countries in 2006 and in the US in 2017.

There is an abundant literature in epidemiology on antibiotic resistance that has documented the increase in resistance (Thung et al. (2016)) as well as trends in prescriptions (Van Boeckel et al. (2014)) or in animal use (Van Boeckel et al. (2015)). While the link is well understood as a biological phenomenon, the evidence relating usage of antibiotics and resistance has been mainly established through ecological studies in epidemiology consisting of cross-sectional studies across countries (Goossens et al. (2005), Riedel et al. (2007), Megraud et al. (2013), Bronzwaer et al. (2002) or van de Sande-Bruinsma et al. (2008)), in

smaller case studies (Vernaz et al. (2008) or Hammerum and Heuer (2009)) or in small randomized control studies (e.g. Malhotra-Kumar et al. (2007)).

While stressing the importance of antibiotic usage, those studies are limited either because they do not take into account confounders or because their results are difficult to extrapolate to gain national policy insights. The contribution of this paper is to leverage large data on antibiotic resistance, prescriptions and usage in animal production over many years and across US states. This allows to identify the separate contribution of several factors in a triple difference design, allowing to control for area fixed effects and time trends that could confound the results. I show that despite the preponderance of antibiotic usage in animal production, antibiotic resistance is mainly driven by prescription in humans and the link between prescription and resistance is particularly strong for the newest classes of drugs.

I. Data

Data on antibiotic resistance comes from the assembly of datasets obtained from the National Antimicrobial Resistance Monitoring System (NARMS), the National Healthcare Safety Network (NHSN), the Gonococcal Isolate Surveillance Project (GISP) and the Tuberculosis Surveillance Systems (TSS). The data record the percentage of specific bacterias that are resistant to a specific antibiotic in a given year and US state. The data that has been assembled for the analysis report information on 15 different bacterias and 13 classes of antibiotics. Those are listed in Table 1 in the appendix. Resistance in bacteria varies between zero for *Mycobacterium tuberculosis* to up to 60 percent for *Acinetobacter*. For antibiotic classes, resistance ranges from 0.8 percent (oxazolidinones) to 23 per-

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cent for tetracyclines. The data span the years 1996 to 2015.

Data on antibiotic prescription was obtained from the National Ambulatory Medical Care Survey (NAMCS), the National Hospital Ambulatory Medical Care Survey (NHAMCS) and IQVIA. By combining these three sources, I obtain a measure of total antibiotic prescriptions by state and year, both in ambulatory care and hospitals. The data span the years 1996 to 2015.

Data on antibiotic usage in animals are obtained by combining state records on the number of animals (classified as cattle, swines and poultry), together with aggregate data on antibiotic usage by type of antibiotics and type of animals (US FDA (2016)). The usage of antibiotics in animal is regulated (and banned in the US since 2017). Not all antibiotic classes prescribed for humans are in use in animal production. The most used class are tetracyclines, but there is considerable variations across animals. Lincosamides are used mainly in swines, while penicillins are mostly used for poultry. This variation, combined with the specialisation of US states in terms of animal production provides stark differences in usage of different antibiotics across the US territory and time.

Figure 1 displays the aggregate trends in antibiotic resistance in humans, together with antibiotic usage in humans and animals. Since 1996, resistance has increased by about 30 percent. At the aggregate level, antibiotic use in animals correlates well with resistance. There is a significant upward trend, with an increase of up to 50 percent, with a recent decline in usage since 2015. In contrast, the use of antibiotics for humans has declined over the sample period, although the aggregate trend masks considerable differences among antibiotic classes. While the prescription of penicillins has decreased, the use of quinolones and tetracyclines has increased.

II. Analysis

Denote by R_{bast} the percentage of resistance of bacteria b for antibiotic a in state s in year t . Denote A_{bast}^H and A_{bast}^A the

amount of antibiotic used for humans and animals respectively. I model the resistance as a function of past usage of antibiotics, of state varying characteristics, state and time fixed effects as well as bacteria*antibiotic fixed effects:

$$R_{abst} = \beta^H A_{bast-1}^H + \beta^A A_{bast-1}^A + X_{st-1}\gamma + \lambda_{a,b} + \lambda_s + \lambda_t + \varepsilon_{bast} \quad (1)$$

The state characteristics include the per capita state GDP, the log of the state population, the share of African-Americans, the share of people below 18 or above 65. The identification of the effect of antibiotic prescription in humans and in animals relies on a triple difference in difference design. This allows to take into account geographical or institutional differences correlated both with antibiotic use and resistance, as well as trends that could confound the relationship. For the baseline specification, I cluster the standard errors at state level, allowing correlated shocks for different bacteria and antibiotics. The regressions are weighted by the number of isolates which are tested. The results are displayed in Table 1.

Column (1) of Table 1 presents the estimated model without antibiotic prescriptions and restricting the time dummies to a linear trend. The results show a significant upward trend in antibiotic resistance over the period of analysis, equal to 0.2 percentage points per year. I next investigate some of the determinants of this increase. Column (2) include the antibiotic prescriptions in humans and in animals. Both variables have been transformed into z-scores. I find a significant effect (at the one percent confidence level) of prescriptions for humans. A one standard increase in antibiotic prescriptions increases the resistance by about 0.5 percentage terms. In contrast the effect of antibiotics in animals, while positive, is much lower and not significant at any conventional level. The next columns of Table 1 probe these results. I first allow for two-way clustering of the standard errors, at state level but also at specific bacteria level. While the standard errors become larger, the effect of antibiotics for

humans is still significant at the conventional 5 percent level. Column (4) introduces further time effects in the form of state specific trends, in addition to aggregate time effects and the state specific characteristics. The results remain similar to the baseline results. Column (5) uses a Tobit specification, as a number of the resistance measures are recorded as zero percent and some at 100 percent. In this specification, I find a larger effect for human prescriptions. Column (6) presents instrumental variable estimates, where human prescriptions are instrumented with temperatures in the specific state. Although antibiotic prescriptions are lagged one year, it is possible that public health authorities put pressure on the medical profession to prescribe less antibiotics in anticipation of increased resistance. I use weather shocks (number of heating and cooling days in a year for a given state) as instruments for antibiotic prescriptions. Adverse weather shocks favor the spread of viruses (see for instance Adda (2016)), which can trigger bacterial infections for which antibiotics are prescribed. The first stage regression confirms this relationship, with an F test of 7 and an associated p-value of 0.002. The exclusion restriction imposes that temperature in the past year does not directly affect the resistance of bacterias to antibiotics. The effects are largely unchanged compared to the baseline. A test for the endogeneity of lagged prescriptions in human does not indicate a significant endogeneity. Finally, column (7) introduces heterogeneous effects by allowing differences between drugs by the date of introduction into the US market. The introduction dates range from the mid thirties for sulfonamides to the early 2000s for lipopeptides. There is considerable heterogeneity, with the use of more modern antibiotics in human prescriptions having the largest effect on resistance. Again, the results for animal use is not statistically significant.

III. Conclusion

This paper leverages the many data on antibiotic resistance across time, US states,

bacterias and antibiotic drugs. Pooling those data together, the analysis allows for a general characterisation of the effect of antibiotic usage, both in humans and in animal farming and to analyze their relative contributions. By employing a triple difference in difference specification, the analysis allows to control for many confounders both at local level and over time that plague traditional ecological studies.

During the period of analysis, bacterial resistance to antibiotics has significantly increased. I find a significant effect of antibiotic prescription for humans, In contrast, the usage of antibiotics in animal farming, has a positive albeit small and statistically insignificant effect on resistance. The results indicate that greater emphasis should be placed on the prescriptions of antibiotics for humans and that resistance is more sensitive to the use of the newest drugs. Unfortunately, those are often the last line of defence against resistant bacteria.

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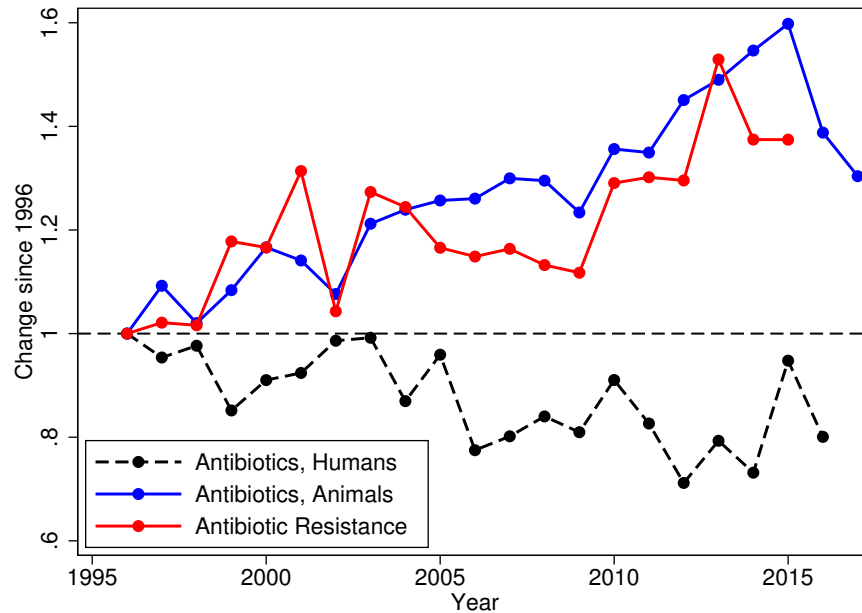


FIGURE 1. AGGREGATE EVOLUTION OF PRESCRIPTIONS AND RESISTANCE

Note: Series normalised to one in 1996.

Source: NARMS, NACM, NHACM and USDA.

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TABLE 1—RESULTS

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Antibiotics humans		0.515*** (0.094)	0.515** (0.253)	0.569*** (0.095)	0.741*** (0.109)	0.489** (0.223)	5.692*** (1.531)
Antibiotics humans*Years since introduction							-.066*** (0.019)
Antibiotics animals		0.059 (0.24)	0.059 (0.285)	0.002 (0.241)	0.264 (0.214)	0.135 (0.231)	3.335 (7.674)
Antibiotics animals*Years since introduction							-.047 (0.11)
Trend	0.207*** (0.075)						
Observations	23,722	21,137	21,137	21,137	21,137	20,343	21,137
Estimation method	OLS	OLS	OLS	OLS	Tobit	IV	OLS
Bacteria*antibiotic FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year FE	No	Yes	Yes	Yes	Yes	Yes	Yes
State FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
State linear trends	No	No	No	Yes	No	No	No
Clustered std. errors	State	State	State and bacteria	State	State	State	State

Note: This table displays estimates of equation (1) in the text. Each column presents estimates from a separate regression. The dependent variable is the fraction of resistant bacterias. Variables on antibiotic usage have been standardized. All regressions are weighted by the number of isolates which are tested. All regressions include log state GDP, log state population, the share of people below 18 and above 65 and the share of African-Americans. FE stands for fixed effects. ***, **, and * denote significance at the 1%, 5%, and 10% levels, respectively.

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