

Superbug Stories

Neha Deopa^{*1}

¹The Graduate Institute of International and Development Studies, Geneva, Switzerland.

Abstract

Antimicrobial Resistance is one of the biggest global public health threats today. Although misuse of antibiotics is an important driver, it is a complex problem that is interlinked with the wider environment, especially with agriculture. In this paper I show, within the context of England, that intensive livestock farming plays a significant role in driving antimicrobial resistance in humans. I then show that poverty is a crucial factor influencing this relation, with higher poverty magnifying the effect intensive farming has on resistance. Finally I document agricultural pollution and contamination via ready to eat meals, as potential mechanisms underlying the transmission from intensive farms to humans.

JEL Codes: I1, I3, Q18

Keywords: Antimicrobial Resistance, Antibiotics, Intensive Farming, Livestock

“May I ask whether we have all gone mad to want to give penicillin to pigs to fatten them? Why not give them good food, as God meant them to have?” - Colonel Gomme-Duncan MP 1953

^{*}neha.deopa@graduateinstitute.ch

1 Introduction

Antimicrobials are drugs that destroy disease causing microbes or pathogens such as bacteria, viruses, parasites and fungi. The most common and predominant of the antimicrobials are antibiotics which treat bacterial infections, others combat viral and parasitic diseases such as AIDS, malaria, Chagas disease etc. Antimicrobial resistance (AMR) occurs when pathogens evolve mechanisms that protect them from antimicrobials, essentially rendering the antibiotics to be ineffective. This allows strains of microbes that are capable of surviving exposure to a particular drug to grow and spread due to a lack of competition from other strains. This has led to the emergence of *superbugs* such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and extremely drug-resistant tuberculosis, bacteria which are difficult or impossible to treat with existing medicines.

The rising rate of AMR is a global health concern, increasing the cost of healthcare by endangering our ability to treat common infectious diseases. This results in prolonged illness, disability, hospitalisation and medication. Recent estimates show that more than 670,000 infections occur in the EU due to antibiotic resistant bacteria, and approximately 33,000 people die as a direct consequence of these kinds of infection (Cassini et al. (2019)). Moreover, the AMR related cost to the healthcare systems is estimated to be around EUR 1.1 billion (ECDC (2018)). The problem for developing countries is even further amplified. If unaddressed, AMR could have a global economic impact of more than \$ 1 trillion annually after 2030 (Adeyi et al. (2017)).

In the past, resistant infections were associated primarily with hospital settings, but over the last decade they have been observed in the wider community. A growing body of evidence has shown that AMR in humans is not only due to direct consumption of antimicrobials but is also inter-linked with AMR in the wider environment and in other populations, especially livestock (Van Boeckel et al. (2015); De Vries et al. (2018); Van Boeckel et al. (2019)). Modern livestock production practices are associated with frequent and abundant use of antimicrobials for growth promotion and prophylaxis. Gilbert et al. (2015) and Tilman et al. (2011) highlight that increase in poultry and pork production has been achieved primarily by intensifying farming: increasing animal densities, using more concentrated feeds and the widespread use of antimicrobials. This includes the use of antibiotics classed as “critically important” for humans by the World Health Organisation.

Animal and human health have increasingly become interlinked through emerging infectious diseases, zoonoses, and antimicrobial resistance. The contribution of farm antibiotic use to human AMR is widely recognised (Laxminarayan et al. (2013); Woolhouse et al. (2015)) and World Health Organisation has emphasised that the high volume of antibiotics used in livestock contributes to the development of resistant bacteria, espe-

cially in settings of intensive production. In the UK and across Europe, vast quantities of antibiotics are still used in agriculture, especially for poultry and swine farms. This cross-species transmission can occur through food, direct contact between humans and animals, or via diffusion into the wider environment and shared sources such as contaminated water and soil. In 2015, an investigation by The Guardian, a British newspaper, showed UK origin pork to be infected with a livestock strain of MRSA, found primarily in intensively reared production animals, from where it can be transmitted to humans.¹

In this paper I aim to study the following questions: Does intensive livestock farming have a significant role in driving AMR in humans? What are the possible mechanisms via which this transmission can occur? To answer to this question, I focus on England which has a surveillance programme for antimicrobial utilisation and resistance in place under its 5-year AMR strategy. I combine three main sources of data covering the 151 counties and unitary authorities across England between 2015 and 2019. Using the surveillance information provided by the Public Health of England, I obtain quarterly AMR and antibiotic consumption estimates for each county. For intensive farming, I use 2010 information on the spatial density of intensively farmed poultry and pig and combine this with time varying geo-localized data on the intensive farming permits issued by the Environmental Agency. Equipped with this data, I estimate how the AMR rates in counties with varying levels of baseline density of intensive farming respond when a new intensive farming permit is issued. I exploit the baseline variation across counties in the number of chickens and pigs farmed intensively per square kilometre and the spatial and temporal variation in the issuance of the farming permits to identify how changes in intensive farming activity, over time and across counties may affect AMR.

I document that while human antibiotic consumption does have a significant role, increasing the number of intensive farming permits issued also has a significant and positive effect on the AMR rates. I also find that as intensive farming density increases, the effect that issuing one permit has on AMR is amplified for counties with high levels of poor households. This corroborates with literature highlighting the role of poverty-driven practices such as poor sanitation in the spread of AMR (Planta (2007)). I then explore three plausible channels through which the intensive farming activities might affect antimicrobial resistance in humans. The first is connectivity, as travel and mobility are important modes of acquisition. Second is diffusion via agricultural pollution such as contamination of soil and waterways by livestock waste and emissions. The last channel is consumption of ready-to-eat meals since contamination of meats during slaughter and processing may leave resistant bacteria and antibiotic residues. My results point to the last two channels as being viable mechanisms.

The aim of this study is not to demonstrate direct causality as it is difficult to

¹The article can be accessed at Wasley et al. (2016)

establish due to the ecological nature of antibiotic selection pressure. While exploring these questions my intention is to highlight significant relations that may bring to light how certain activities, such as intensive farming which is characterized by high usage of antibiotics, can in fact amplify pathways of exposure to AMR for humans. These results can shed light on the underlying drivers, transmission and impact of AMR in the wider environment and food chain which remains poorly understood. The UK Five Year AMR Strategy (2013–2018) specifically recognized the need for further research and evidence to improve understanding of the different transmission pathways. Assessing the level of AMR in the environment and its link with humans and animals is an important health domain for the UK over the next five years. Thus my results are extremely relevant for public policy intervention.

The only two other papers that explore AMR within the economic literature are Innes et al. (2020) and Adda (2020). Both are within the context of the United States and the former develops a model to quantify the external costs of antimicrobial use in animal agriculture on antimicrobial resistance in humans and finds a cost of \$1500 per kilogram of enrofloxacin (a class of “critically important antibiotics” for humans) used for poultry. The latter uses data on antibiotic resistance, prescriptions, and usage in livestock and finds that despite controlling for antibiotic usage in animal production, AMR is mainly driven by human prescriptions. Although my results corroborate with both papers on the role of human antibiotic consumption, my results vary from Adda (2020) with respect to the role of livestock. This maybe due to the fact that by only examining antibiotic usage in animal production, the sole channel that is being captured, via which AMR could be affected, is by means of direct contact. On the contrary, I study the role of intensive farming activity as a whole, which is able to account for all potential pathways through which AMR could be transmitted in the community. However, my specification has the underlying assumption that intensive farming activity automatically equates to usage of antimicrobial use. I discuss in detail in Section 2.1 why this is not an unreasonable assumption.

The rest of the paper is organized as follows. Section 2 gives background on the intensive farming sector and the current state of AMR in England. Additionally, I discuss the channels through which intensive production of livestock can impact AMR in humans. Section 3 present the data and descriptive statistics and section 4 outlines the empirical strategy. Section 5 and 6 contains respectively the main results and the test of the suggested channels. The last section concludes.

2 Background

2.1 Intensive livestock farms as reservoirs of AMR

Evidence suggests that global consumption of antimicrobials in animals is twice that of humans, with 73% of all antimicrobials sold globally being used in livestock (Van Boeckel et al. (2015); Van Boeckel et al. (2019)). Farming in an intensive, commercial production system is highlighted by its excessive use of antibiotics. The most controversial of the practices is growth promotion where the aim is not to maintain the health of the livestock but rather to routinely add antimicrobials to animal feed in low doses to promote faster growth in healthy animals. Although this has been banned in the EU and UK since 2006, the practice of prophylaxis (when antibiotics are used for disease prevention) and metaphylaxis (if a disease spreads quickly a vet can make a clinical judgement to treat all of the animals in a pen) continues to be legal and is used extensively in intensive poultry and pig farming (Lunha et al. (2020); O'Neill et al. (2016)).

As reported by The Guardian, based on Environmental Agency data, UK saw a rise in industrial-sized pig and poultry units by 7% from 1,669 in 2017 to 1,786 in 2020, with England accounting for 1,313 intensive farms. Poultry accounts for majority of these with 1,092 followed by 221 pig farms. In 2017 the total antibiotic consumption in UK, for both humans and animals, was 773 tonnes. 26% of this was authorised for use in food-producing animals only and included the use of some WHO listed High Priority - Critically Important Antimicrobials (HP-CIA) for humans, with poultry and pig once again leading in this aspect. Table A.1 in the appendix provides a list of the latest HP-CIA published by the WHO.

The poultry industry frequently uses antibiotics for the treatment and prevention of respiratory diseases and other bacterial infections, which are often administered via their drinking water. UK poultry farmers continue to use the class of HP - CIA *fluoroquinolones* even though its use has been banned in the US chicken farms explicitly due to dangers of human infections of fluoroquinolone-resistant *Campylobacter* species² associated with consumption of poultry. Similarly, the UK pig industry has a particularly high use of antibiotics. In 2017, their antibiotic usage was 131 mg/kg while the government's target for farm antibiotic is at 50 mg/kg.³ According the reports by Alliance to Save Our Antibiotics, an overwhelming majority of use in pig farming is for group treatments and for intensive, indoor systems they often receive antibiotic treatment at each stage of their lives until slaughter.

²*Campylobacter jejuni* is one of the most common causes of food poisoning in Europe and in the United States.

³These are based on the European livestock unit: population correction unit (PCU)

There is strong evidence suggesting that antibiotic use in animals is an important factor in promoting resistance in humans. Vieira et al. (2011) find that for eleven European countries the resistance in *E. coli* isolates from food animals (especially poultry and pigs) was highly correlated with resistance in isolates from humans. Several other studies have shown similar results highlighting that even drugs used therapeutically in livestock may in fact generate a reservoir of antibiotic resistant bacteria, threatening the efficacy of human drugs (Smith et al. (2002); Ward et al. (2014); Liu et al. (2016)). The possibility of this is amplified in an intensive farm setting where animals are particularly vulnerable to pathogens and the high densities facilitate the transmission of diseases (Gilbert et al. (2015)). Although farm antibiotic use in the UK has been cut by about 50% between 2014 and 2018, there is little evidence of significant changes to husbandry aimed at improving animal health and reducing the incidence of disease which is often the cause of excessive use of antimicrobials for prophylaxis.

2.2 AMR in Humans in UK

The UK has had a national strategy to combat AMR since 2000 and in 2013 they integrated their action plan with a “One Health” approach which aims at tackling resistance across both human and animal health. This has led to several encouraging outcomes such as a 7.3% reduction in antibiotic use in humans and a reduction of 40% in food-producing animals⁴. However, despite these efforts Public Health England has stated that about 20% of all antibiotics prescribed in primary care in England are inappropriate and one in every three individuals take at least one course of antibiotics each year (Report (2019)). According to the latest English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) between 2015 and 2019 the UK saw a 32% increase of antibiotic resistant blood stream infection (BSI) from key bacterial species such as *Escherichia coli* (*E. Coli*). Essentially in 2019, 21 out of every 100 people having a pathogen BSI had a resistant infection. This has become a major public health concern, since rates of resistant BSI are increasing not only in UK but also across Europe (Vihta et al. (2018)).

2.3 Diffusion into the Wider Environment

Increasing rates of AMR in humans has been associated with the environmental diffusion of antibiotics and resistant bacteria and their propagation occurs via multiple pathways in the ecosystem (He et al. (2020); Checcucci et al. (2020)). The infographic seen in Figure 1 provides an excellent overview of various pathways of how resistance can spread. Aside from the direct consumption of antibiotics, within health facilities resistant bacteria can

⁴This estimate is based on use per ‘bodyweight’,

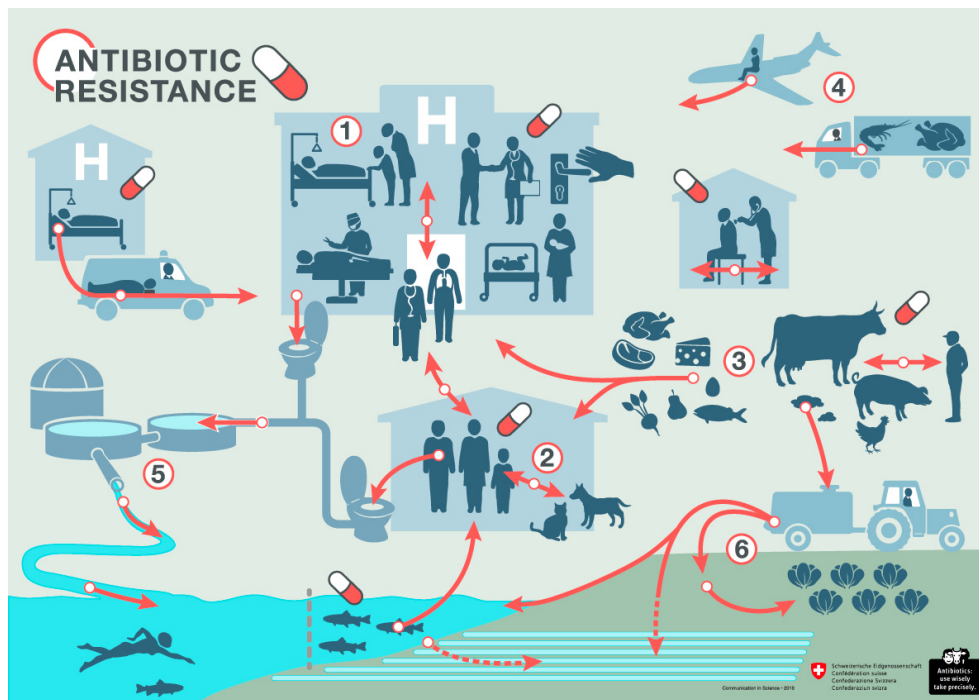


Figure 1: A Complex Web: Everything is Connected. Source: Swiss Federal Office of Public Health

be transmitted through contact between patients, visitors and medical staff. Mobility plays an important role as well, since tourism and food imports are the fastest way of spreading resistant bacterial strains across national and local borders.

From the perspective of intensive farming there are several crucial diffusion mechanisms. Although there is the possibility of direct transference from human to animal, or vice versa, the prominent channel is thought to be via agricultural pollution (O'Neill et al. (2015)). Antimicrobial use in livestock is administered primarily via feed or water and much of this is excreted un-metabolised, entering sewage systems, water sources and soil. Therefore, animal waste not only contains resistant bacteria, but also antibiotics that could contribute to the emergence of resistance in bacteria beyond those existing in the animal. The livestock manure and slurry is often used as fertilisers for crops, leading to further dissemination of antibiotic residues and resistant bacteria in the soil-water system, food crops and the wider environment. Stormwater and irrigation water from farms can also contaminate nearby lakes and rivers.

Another important route is when animals are slaughtered and processed for food, the resistant bacteria in the animal gut can contaminate meat or other animal products. This often leads to people getting sick from eating or handling contaminated food. According to the 2016 study conducted by The Alliance to Save our Antibiotic, one in four samples

of chicken from UK’s largest supermarkets⁵ contained antibiotic-resistant E.Coli bacteria. Additionally, a total of 19% of the E. coli from pork and poultry samples were resistant to a HP-CIA gentamicin, used to treat serious bacterial infections.

Acknowledging the complex interactions and spread of AMR across different sectors such as communities, hospitals, farming animals and because environmental reservoirs are a potentially important source for the mobilisation and transfer of resistance bacteria, WHO has emphasized an integrated and multisectoral “One Health” approach to tackle AMR.

3 Data

3.1 Antimicrobial Consumption and Resistance in Humans

I use data provided by the Public Health of England on the Fingertips database which gives access to a wide range of health related indicators for England. These data are provided at the lowest level of the English health geography which is the Clinical Commissioning Groups (CCG). For ease of comparison with other data, I match them to the administrative geography level of the 151 counties and unitary authorities as at April 2019. Under the domain of AMR local indicators I focus on:

- **Rolling quarterly average proportion of E. coli blood specimens resistant to ciprofloxacin; by quarter:** This is the main AMR indicator and used as the outcome variable in the empirical analysis. This indicator demonstrates the rolling average quarterly proportions of ciprofloxacin resistance in a patient identified as having E. coli blood specimens, which is then tested for susceptibility in each CCG. Ciprofloxacin is one of the most widely used antibiotic from the class of fluoroquinolone antimicrobial drugs. Fluoroquinolones are HP - CIA used to treat serious human infections when other antibiotics have not worked. This includes cases of complicated urinary tract infections, gastrointestinal infections, sexually transmitted diseases, and respiratory tract infections. In food producing animals, fluoroquinolones are used for prophylaxis and metaphylaxis to treat intestinal infections and respiratory diseases. There is an increasing public health concern that the use of these drugs in livestock selects for bacterial resistance that can be transmitted into the food chain (Schulz et al. (2019)). Poultry especially are recognised as an important source of these infections in humans and the use of fluoroquinolone has been banned in the US for this very reason (Nelson et al. (2007))

⁵Asda, Aldi, Co-op, Morrisons, Sainsbury’s, Tesco and Waitrose.

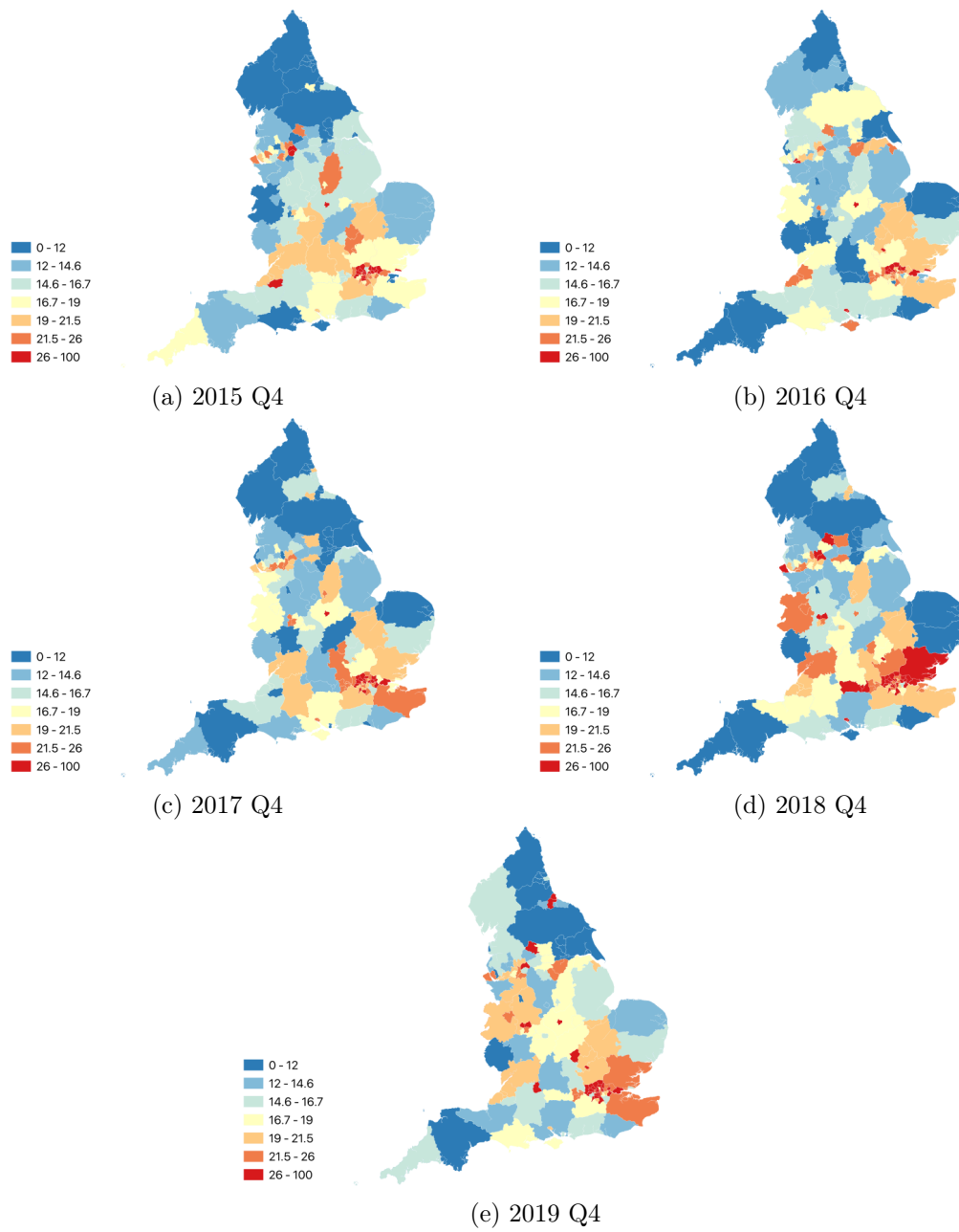


Figure 2: Evolution of AMR in humans in England

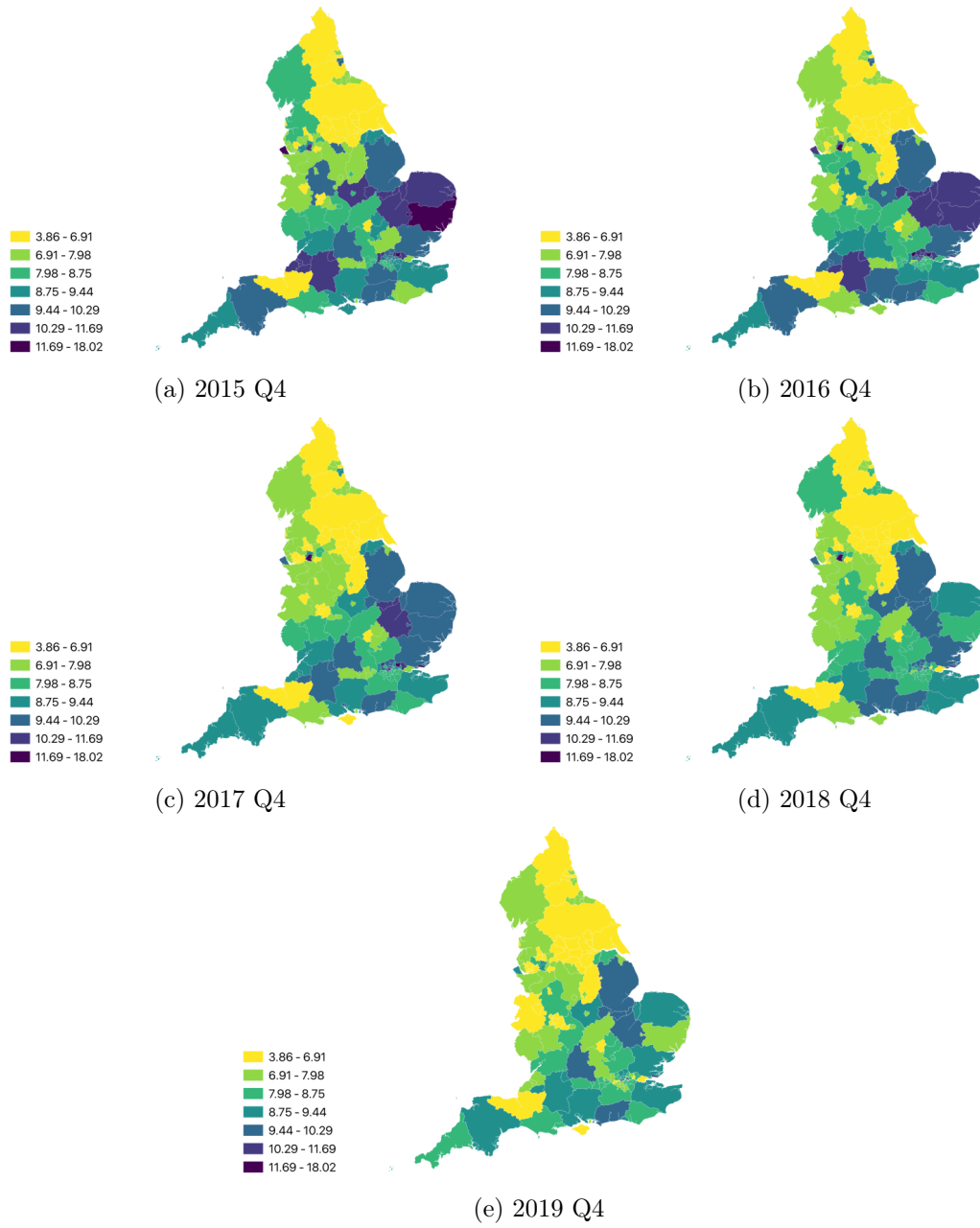


Figure 3: Evolution of percentage of prescribed antibiotics in England

but continues to be used in the UK.

Although there are different approaches to assess the prevalence of AMR, E.Coli is a bacteria which can serve as an important gauge of resistance in the food chain as it is found in the intestines of both humans and animals. Therefore, E. coli often serves as an indicator for AMR in livestock as well as humans for surveillance programmes and to investigate dynamic population changes. Moreover, as stated in the 2019 UK One Health Report, E. coli was the most common bacterial cause of bloodstream infections in people in 2017 which led to the government intensifying its focus on this indicator. Specifically as ciprofloxacin resistance in E. coli is a key combination highlighted as part of the government 5-year antimicrobial resistance strategy, continuous monitoring has been recommended.

Presented as a rolling quarterly average across a 4 quarter period, I use data for 2015 Q4 - 2019 Q4. Figure 2 shows the evolution of AMR in England for selected quarters.

- **Percentage of prescribed antibiotic items from cephalosporin, quinolone and co-amoxiclav class by quarter:** This shows broad-spectrum antimicrobials: cephalosporin, fluoroquinolone and co-amoxiclav, prescribed in a quarter. All three represent classes of HP-CIAs. This indicator is a part of the UK government’s five-year National Action Plan 2019-2024 to reduce antimicrobial use in humans by 15% by 2024. Similar to the AMR indicator, I use data for the time period 2015 Q4 - 2019 Q4. Figure 3 shows the evolution of the prescribed broad-spectrum antibiotics in England for selected quarters.

3.2 Intensive Farming

As there is no direct monitoring of intensive farming systems in UK, in order to assess the impact of intensive livestock on AMR in humans, I combine two data sources. Gilbert et al. (2015) disaggregate existing FAO spatial global livestock distribution maps into 10 km resolution maps of chicken and pig distributions into extensive and intensive systems for 2010. Figure A.2 in the appendix shows the global distribution of chickens and pigs farmed in intensive systems per square kilometre. Using this data I find the average density of chickens and pigs farmed intensively for counties in the UK for 2010, as seen in panel (a) of Figure 4.

The second source I use is information on the number of intensive farming permits issued by the Environmental Agency (EA). In the UK, farms are classified as intensive if it “rears pigs or poultry in an installation with more than 40,000 places for poultry, 2,000 places for production pigs over 30kg or 750 places for sows”.⁶ EA licenses business

⁶While intensive pig and poultry facilities require a permit from the EA, this is not obligatory for

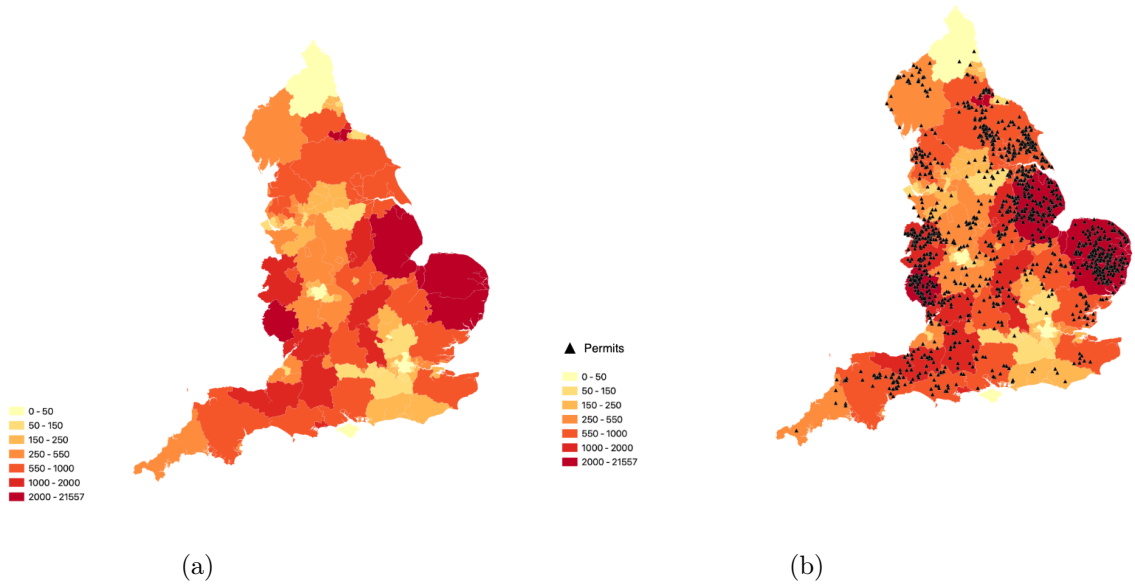


Figure 4: Panel (a): Average density of chickens and pigs farmed intensively per square kilometre in 2010. Panel (b) New intensive farming permits issued between 2004 and 2020

and individuals to carry out certain activities that have the potential to pollute the environment and the installation of intensive farms falls within this purview. They have a public registry of permits issued containing details of the farm operator, the issuance date and the site location. Panel (b) of Figure 4 shows all the permits that have been issued in England since 2004 up until 2020. I match these permits to the county and quarter they were issued in, for the period 2015 Q4 - 2019 Q4, as seen in Figure 5. One can observe there is substantial variation across and within counties in the number and timing of when the permits were issued.

3.3 Other Variables

For additional controls I include a set of time varying socio-economic and demographic variables at the county level. I control for the share of population below 15, above 65, the share of ethnic minority, log of the population, employment rate and median weekly earnings. Additionally, to capture aspects of inequality and poverty I include the percentage of people resident in the county living in each national deprivation quintile. This is based on an Index of Multiple Deprivation which is the official measure of relative deprivation in England.⁷ The difference in deprivation between areas is a major determinant of health inequality in the United Kingdom. All this information is publicly available by

intensive beef and dairy units, hence my analysis excludes this sector.

⁷The indicator comprises of seven distinct domains: Income Deprivation, Employment Deprivation, Health Deprivation and Disability, Education, Skills and Training Deprivation, Barriers to Housing and services, Living Environment Deprivation and Crime

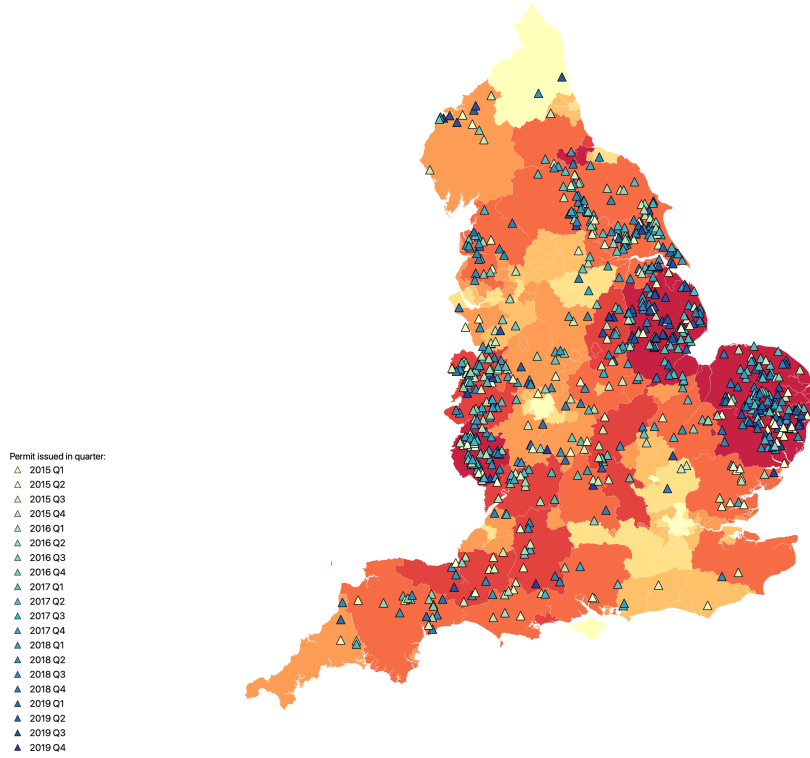


Figure 5: Density of pigs and chickens and the new intensive farming permits issued between 2015 Q4 and 2019 Q4

the Office for National Statistics and Public Health England. For instrumental variable estimation, the information on the international price of wheat and poultry is retrieved from FAO Food Price Monitoring and Analysis Tool. The data for monthly temperature has been obtained from HadUK-Grid, a new dataset of gridded climate observations for the UK produced by the Met Office Hadley Centre for Climate Science and Services.

For data on Nitrogen oxide pollution I use annual background pollution maps at 1x1 km resolution, provided by the Department for Environment, Food and Rural Affairs. Connectivity and journey time statistics have been obtained from the Department for Transport. Finally, data on household expenditure on food purchased outside the home such as takeaways and sandwich shops, is taken from the UK household longitudinal survey by The Understanding Society. Table 1 contains descriptive statistics on the final sample.

Table 1: Descriptive Statistics

Variable	N	Mean	St. Dev.	Unit
AMR	2,567	18.8	7.2	%
Antibiotics prescribed	2,567	8.7	1.839	%
Intensive farming permits	2,567	0.3	1.2	Absolute value
Intensive farming density	2,550	585	1.819	No of birds and pigs per km ²
Population below 15	2,567	70,640	52,505	Absolute Value
Population above 65	2,567	66,808	60,062	Absolute Value
Total Population	2,567	369,067	277,851	Absolute Value
Employment	2,550	74.5	4.8	%
Ethnic minority	2,534	15.5	15.4	%
Median Weekly earnings	2,527	567.7	87.4	£
Traffic volume	2,567	3,165	3,359	Million vehicle km.
Living in most deprived quintile	2,533	23.1	17.4	%
International Price of Wheat	2,567	216.6	17.1	\$/tonne
International Price of Poultry	2,567	960.2	68.4	\$/tonne
NO _x & NO ₂	2,567	22.9	14	µg/m ³
Avg. monthly expenditure on food outside home	2,012	85.7	47.9	£

4 Empirical strategy

I turn now to the empirical analysis, estimating the following equation:

$$\begin{aligned} \text{AMR}_{cq} = & \beta_1 \text{Ant}_{c,q-i} + \beta_2 \text{Permit}_{c,q-i} + \beta_3 \text{Permit}_{c,q-i} \times \text{Int}_{c,2010} \\ & + \delta \mathbf{X}_{cq-i} + \alpha_c + \theta_q + \psi_{rq} + \epsilon_{cq} \end{aligned} \quad (1)$$

where (c, q) denote the county and quarter, and i is the period of lag. The dependent variable, AMR_{cq} is the rate of antimicrobial resistance shown by ciprofloxacin resistance in a patient identified as having E. coli blood specimens, at county-quarter level. Consistent with epidemiology literature and Adda (2020), I model AMR as a function of past usage of antibiotics and past activities and exposure to intensive farming and county-varying characteristics. Therefore, my explanatory variables are lagged. Although the literature states that building resistance is a gradual process, there is no defined period. Hence I explore my specification for $i = 4, 8$ which indicates a lag of one and two years. $\text{Ant}_{c,q-i}$ is the percentage of broad spectrum antibiotics prescribed and $\text{Permit}_{c,q-i}$ is the number of intensive farming permits issued. $\text{Int}_{c,2010}$ represents density of intensive farming i.e. the amount pigs and poultry farmed per square kilometre for each county in 2010, which is five years prior to our sample time period of 2015 Q4 - 2019 Q4. $\mathbf{X}_{c,q-i}$ is a vector of controls that includes the share of population below 15, above 65, the share of ethnic minority, log of population, employment, earnings and deprivation.

In equation (1) my primary coefficient of interest is β_3 which is the interaction between baseline intensive farming in 2010 and the number of intensive farming permits issued since 2015 Q4. This coefficient captures the impact on AMR of an increase in

the number of intensive farming permits issued in counties with varying levels of existing intensive farming density. The secondary coefficient of interest is β_1 showing the effect of human antibiotic consumption. Throughout the paper, standard errors are wild cluster bootstrapped at the county level.

To isolate the effect of intensive farming I exploit the spatial and temporal variation in the issuance of permits and the baseline intensive farming density. I include county fixed effects α_c to account for any time-invariant differences in AMR across counties, and quarter fixed effects θ_q to control for the common evolution of AMR in all counties in any give quarter. Additionally, I also control for region by quarter fixed effects ψ_{rq} which capture non-linear time trends specific to each of the nine regions across England. This specifically accounts for factors such as regional differences in agricultural characteristics affecting livestock farm incomes and operating costs. All information related to English farm accounts is published in the annual Farm Business Survey which is conducted at regional geography and hence should be absorbed by these set of fixed effects.

5 Results and Discussion

Column 1 and 2 of Table 2 presents the estimated model with only county and quarter fixed effects. The first column explores the specification with a lag of $q - 4$ where I find a weakly significant and positive impact of the prescription of broad spectrum antibiotics on AMR, however, the interaction term shows no significant effect. In the second column which looks at a lag of $q - 8$ the effect of antibiotics becomes stronger, moreover, our main coefficient of interest on the interaction term is positive and significant. We find that the effect intensive farming permits have on AMR changes based on the baseline level of intensive farming density existing in the county. In column 3, I estimate the model with the full set of fixed effects including region by quarter and find the results to be consistent with column 2. To get a complete picture of the role of intensive farming and to better understand the interaction term, I look at the average marginal effects as shown in Figure 6. I find that in counties where the level of intensive farming density is zero, the issuance of permits has a negative and significant effect. However, as the density increases I find the slope changes and there is a positive and significant relationship between AMR and the number of permits issued.

Although the antibiotic prescriptions are lagged by eight quarters, it is possible that because of National Health Service supported initiatives and government strategy to combat antimicrobial resistance there is an intentional decline in prescribing antibiotics in anticipation of increased resistance. Therefore, similar to Adda (2020), I use weather shocks as instruments. Using the spatial grid temperature data, I calculate the deviation

Table 2: Main Results

	<i>Antimicrobial Resistance in Humans</i>				
	(1)	(2)	(3)	(4)	(5)
Antibiotics $c,q-4$	0.372* (0.211)				
Permits $c,q-4$	-0.219 (0.151)				
Permits $c,q-4 \times$ Int. Farming $c,2010$	0.077 (0.070)				
Antibiotics $c,q-8$		0.408*** (0.158)	0.335** (0.170)	2.325** (0.997)	0.309*** (0.155)
Permits $c,q-8$		-0.307** (0.119)	-0.431** (0.183)	-0.909 (2.923)	-0.157 (0.150)
Permits $c,q-8 \times$ Int. Farming $c,2010$		0.147*** (0.045)	0.175*** (0.065)	0.468** (0.223)	0.053 (0.071)
\times High Poverty $c,q-8$					0.959*** (0.208)
Observations	2,502	2,344	2,344	2,344	2,344
Estimation method	OLS	OLS	OLS	IV	OLS
County FE	Yes	Yes	Yes	Yes	Yes
Quarter FE	Yes	Yes	Yes	Yes	Yes
Region \times Quarter FE	No	No	Yes	Yes	Yes
Additional Controls	Yes	Yes	Yes	Yes	Yes

*p<0.1; **p<0.05; ***p<0.01

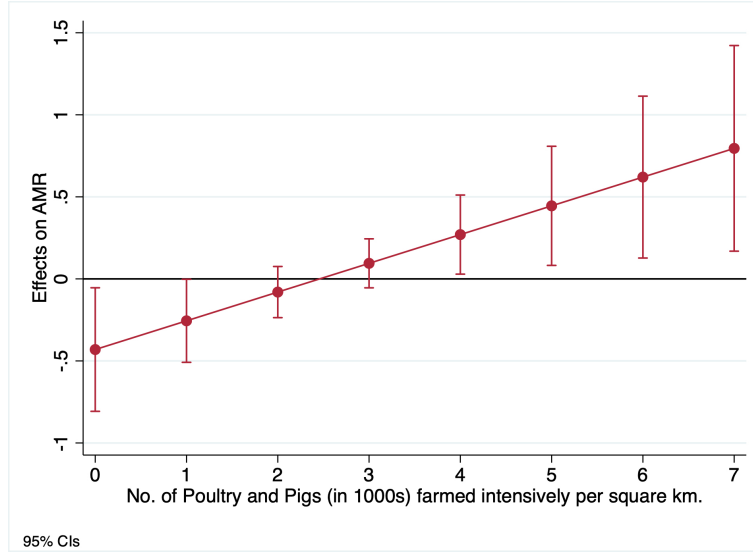


Figure 6: Average Marginal Effect of Intensive Farming Permits Issued

of the county's monthly temperature from its long-term average. If this deviation is below the first quartile or above the third quartile, I classify it as an extreme weather shock. The intuition behind this is from Adda (2016) who highlights that extreme temperature favours the spread of viruses which can trigger bacterial infections for which antibiotics are prescribed.

The second variable that I instrument is the number of intensive farming permits issued, as it is possible that the spatial and temporal variation in their issuance may not be completely exogenous. There may be a tendency by EA to favour counties that already have permits issued in the past or more experience with the system. I use two instruments, first is the international price of wheat which is benchmarked by the US wheat (No.2 Hard Red Winter, f.o.b.) and second is the international price of poultry, which is also benchmarked by the US poultry sector. Cereals and grains are a crucial part of livestock farming as they are used as animal feeds and these prices can impact the entire livestock production cycle (Haley and Mathews (2016)). According to the Agriculture and Horticulture Development Board of UK, the cereal with the highest usage for animal feed is Wheat (largely used by the poultry sector) followed by Barley and Maize. Therefore, any change in their international price will influence the total number of applications for the permits, which in turn will affect the final number of permits issued. Similarly, any change in the world price of poultry is likely to influence permits along the same channel. It is important to note that the UK poultry sector is not a big enough exporter or importer to be able to actually influence these prices. Since I instrument two endogenous variables, the conditional first stage F statistic is 6 and 20 respectively (Sanderson and Windmeijer (2016)).

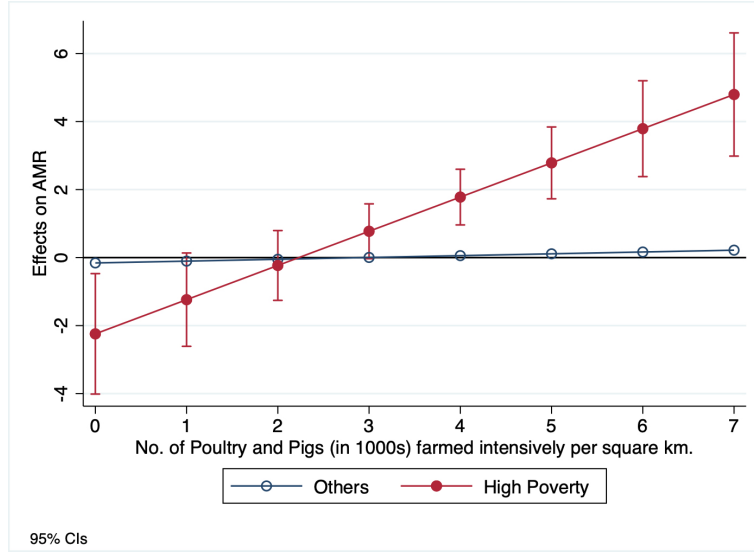


Figure 7: Average Marginal Effect of Intensive Farming Permits Issued based on the Poverty levels of the County

Column 4 presents the IV estimates which once again shows the interaction term to be significant and positive. Thus, a spike in the intensive farming permits increases AMR in counties with pre-existing levels of intensive farming. Additionally, the effect of antibiotics on AMR becomes even stronger. Next I explore how this relation maybe influenced by poverty within the counties. Poverty-driven practices such as overcrowding, poor hygiene and sanitation may amplify the role of intensive farming in driving AMR in humans. I specifically focus on fuel poverty, where a household is considered to be fuel poor if they have above average fuel costs and if they spend this amount their residual income would put them below the poverty line. There is strong evidence linking cold homes with poor health outcomes for all age groups. I introduce a dummy variable where I classify counties as high poverty if the percentage of households that experience fuel poverty is above the third quartile, which for my sample is 12.4%. In equation (1), I interact this with my main interaction term of interest, resulting in a triple interaction. Based on the results in column (5) and Figure 7 I find that the difference in slope between high poverty counties and the rest is significant and positive. As the density increases I find the effect that issuing one permit has on AMR is amplified and positive for areas where the percentage of households which are fuel poor is high.

6 Possible Mechanisms

As discussed in Section 2.3, several mechanisms may underlie my findings. In this section I focus on three specific channels.

Connectivity: Increasing population mobility across borders plays an important role in the globalization of public health threats and risks. A possible channel through which AMR may transmit from the intensive livestock farms to humans is due to increasing travel and tourism, which are important modes of acquisition (Frost et al. (2019)). Therefore, to proxy for connectivity I use annual data on motor vehicle traffic (in ten million vehicle kilometres) and rerun specification (1) while controlling for connectivity of counties. In column (1) of Table 3, connectivity is found to have a positive but weakly significant effect on AMR. Additionally, accounting for this has very little impact on the size and statistical significance of the interaction term.

Table 3: Mechanisms

	<i>Dependent variable:</i>		
	AMR	NO _x	FOOD OUTSIDE HOME
	(1)	(2)	(3)
Permits $c,q-8 \times$ Int. Farming $c,2010$	0.155** (0.063)	0.049** (0.021)	0.017** (0.008)
Connectivity	0.056* (0.031)		
Observations	2,344	2,344	1,828
County FE	Yes	Yes	Yes
Quarter FE	Yes	Yes	Yes
Region \times Quarter FE	Yes	Yes	Yes
Additional Controls	Yes	Yes	Yes

*p<0.1; **p<0.05; ***p<0.01

Agricultural Pollution: The second mechanism I explore is via agricultural pollution. The agricultural sector is the biggest source of ammonia and nitrogen pollution in England, with majority coming from livestock farming (Misselbrook and Gilhespy (2019)). A part of these emissions come from the livestock manures and slurries, stemming from intensive poultry and pork units. This animal waste, which is often used as fertilizers, is an important source of transmission of resistant bacteria and antibiotic residues. Therefore, nutrient and pollution management are important components of intensive livestock practices. Additionally, the manure and slurry are a source of mineral nitrogen (N) which can flow into waterways, have negative effects on biodiversity, or be lost as gaseous nitrous oxide (a greenhouse gas) and nitrogen.

To explore if intensive livestock is influencing AMR in humans via transmission through increased use of slurry and manure and agricultural pollution, I examine the relation between the interaction term and the ambient concentration of Nitrogen Oxides

(NO_x) and Nitrogen Dioxides (NO₂).⁸ In column (2) of Table 3 I re-estimate equation (1) but with the dependent variable being annual mean concentration of NO_x and NO₂ in micro-grams per cubic meter air ($\mu g/m^3$). The positive and significant coefficient on the interaction term provides evidence that agricultural pollution from intensive farming could be a potential channel for AMR transmission from the farms to humans

Ready-to-Eat Meals: An alternative potential diffusion mechanism from intensive farms to humans is via contamination of meats during slaughter. Similar to the examples stated in section 2.3, lack of hygiene and proper sanitary conditions during food processing can result in the final product having resistant bacteria and antibiotic residues. This is of concern especially for ready-to-eat (RTE) meals since they are consumed without further processing and any bacteria and AMR present have an increased probability of coming in contact with the human gut microbiome (Chajęcka-Wierzchowska et al. (2014); Jans et al. (2018); Food Standards Agency (2019)). Currently the Food Standards Agency of UK is conducting a research on this as this could be an important dietary driver of AMR.

To explore the viability of this channel, similar to agricultural pollution, I re-estimate equation (1) but with a dependent variable that captures the consumption of RTE. Using the Understanding Society household longitudinal data, I use the log of average monthly household expenditure (in pounds) on meals/snacks outside the home as a proxy for demand for RTE. This variable includes the amount spent on food bought from takeaways, sandwich shops, work or school canteens but does not include alcohol or super market meals. In column (3) I find a significant and positive effect of the interaction term on the average monthly expenditure on RTE.

Overall, my findings suggest that, while connectivity and mobility may have relatively weak impact on AMR, channels of agricultural pollution and contaminated food maybe a more significant mechanism.

7 Conclusion and Future Work

This paper provides an exploratory analysis of the impact of intensive farming on antimicrobial resistance in humans in England. I find that while human antibiotic consumption does play an important role, increasing the number of intensive farming permits issued also has a significant and positive effect on the AMR rates. I also show that this effect is amplified for counties where there is high percentage of fuel poor households. Additionally I show that there maybe two mechanism driving this relation. First is

⁸Although Ammonia emissions would be ideal, due to lack of recent data, I focus on Nitrogen.

the diffusion via agricultural pollution such as contamination of soil and waterways by livestock waste and emissions. The second is consumption of ready-to-eat meals since contamination of meats during slaughter and processing may leave resistant bacteria and antibiotic residues. In contrast, I only find weak evidence on local connectivity being a viable channel. My results are an important contribution to the policy debate on how to tackle the growing public concern over AMR.

Although the work on this paper is currently preliminary, it can be considered a prelude to future research. This topic is especially relevant because AMR is an emerging health catastrophe which needs to be addressed as soon as possible. There are several empirical and theoretical directions in which this research can be extended. Investigating the transmission mechanisms further will prove to be an important policy exercise. Additionally the next natural step is to develop a bio-economic model to evaluate socio-economic factors affecting the prevalence of human AMR.

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Appendix

A Figures

Antimicrobial class	Example of antimicrobials(s)
CRITICALLY IMPORTANT ANTIMICROBIALS	
Aminoglycosides	gentamicin
Ansamycins	rifampicin
Carbapenems and other penems	meropenem
Cephalosporins (3 rd , 4 th and 5 th generation)	ceftriaxone, cefepime, ceftaroline, ceftobiprole
Glycopeptides	vancomycin
Glycylcyclines	tigecycline
Lipopeptides	daptomycin
Macrolides and ketolides	azithromycin, erythromycin, telithromycin
Monobactams	aztreonam
Oxazolidinones	linezolid
Penicillins (antipseudomonal)	piperacillin
Penicillins (aminopenicillins)	ampicillin
Penicillins (aminopenicillin with beta-lactamase inhibitors)	amoxicillin-clavulanic-acid
Phosphonic acid derivatives	fosfomycin
Polymyxins	colistin
Quinolones	ciprofloxacin
Drugs used solely to treat tuberculosis or other mycobacterial diseases	isoniazid

Figure A.1: High priority antimicrobial classes and example antimicrobial agents used in human medicine

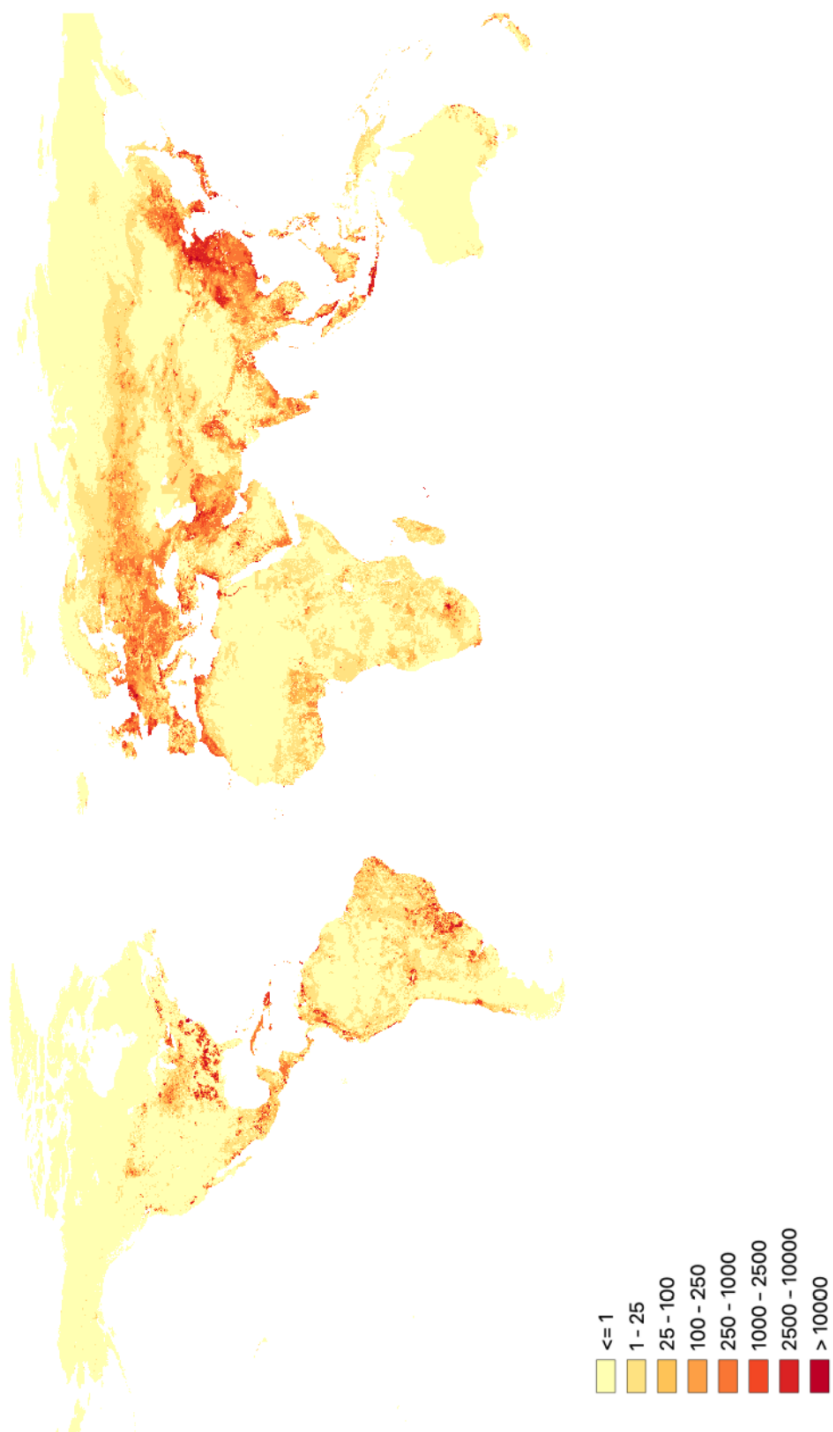


Figure A.2: Chickens and Pigs in intensive systems per square kilometre in 2010