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# FOSFOMYCIN *ESCHERICHIA COLI* RESISTANCE IN POULTRY MEAT ASSOCIATED WITH THE EXCESSIVE USE OF BIOCIDES DURING COVID-19

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## ABSTRACT

**The emergence of antimicrobial resistance has become one of the major public health problems. Although antimicrobial resistance naturally develops over time, its prevalence has increased due to the use of antimicrobial agents in the health sector and other contexts. This paper focuses on the rise in fosfomycin resistance of *Escherichia coli* isolated from poultry meat, coinciding with the excessive use of biocides during the COVID-19 outbreak in Algeria. A total of 134 *E. coli* isolates were identified from poultry meat samples purchased from the same butcher's shops before and after the emergence of the COVID-19 outbreak. Univariate analyses were conducted using the ANOVA test for continuous variables and the chi-squared test for categorical variables. Odds ratios (OR) and 95 % confidence intervals (CI) were utilized for statistically significant risk factors. Multivariable analysis was performed with binary logistic regression to detect an independent predictor. A P-value of 0.05 was considered to indicate statistical significance. Poultry meat purchased after the COVID-19 appearance was found to be associated with fosfomycin-resistant *E. coli*; fosfomycin-resistant *E. coli* isolates were more prevalent after COVID-19 (15.56 %) than before the COVID-19 outbreak (1.69 %). A significant difference in fosfomycin *E. coli* resistance was observed before and after the COVID-19 emergence (P = 0.009; OR = 10.68; 95 % CI 1.26–90.34). *E. coli* strains isolated from poultry meat are 10 times more likely to be fosfomycin resistant after COVID-19 than before the COVID-19 outbreak. It could be that the excessive use of biocides during the COVID-19 outbreak increased the risk of fosfomycin *E. coli* resistance in poultry meat.**

**Key words: antibiotic resistance; biocides; co-resistance; logistic regression; risk factor**

## INTRODUCTION

The crisis of antimicrobial resistance (AMR) is one of the most serious issues facing us today. The fast development and global spread of AMR regardless of the geographical location or community of origin is a truly global problem [42]. Antibiotic resistance-related fatalities will rise from 700,000 to 10 million per year by 2050, surpassing cancer as the leading cause of death, according to the O'Neill report [28].

Antibiotic resistance persists in spite of the restricted use of several key antibiotics, which indicates that there are components governing the evolution, dissemination and perpetuation of these resistance systems, many of which are independent of antibiotic usage [3, 41]. Recent studies suggest that the exposure to sub-inhibitory biocide concentrations facilitates the evolution of resistance to the biocide, and may also lead to co-resistance and cross-resistance to other antimicrobial agents such as antibiotics [10]. Repeated exposure of bacteria to certain microbicides (biocides) *in vitro* can result in decreases in antimicrobial susceptibility [9]. The inappropriate (over/misuse) use of antibiotics (and disinfectants/biocides) in many 'One Health' areas such as human health and hygiene, agriculture, animal husbandry and food production industries are major contributing factors in the emergence of AMR (or disinfectant/biocide resistance) in the last century [1].

The emergence of the COVID-19 (Coronavirus disease 2019) pandemic has further complicated the current and future landscape of global AMR. The COVID-19 pandemic is predicted to impact the transmission of bacterial infections and the emergence of AMR [34]. The outbreak of COVID-19 in 2020 has contributed to the rising use of antibiotics and biocides [13]. Intensified cleaning protocols during the COVID-19 pandemic specifically call for the increased use of disinfectants in homes and high-risk public spaces, such as schools, health and other care facilities, and food service and work spaces [7].

Bacterial resistance to biocides used as antiseptics, dyes, and disinfectants is a growing concern in food preparation, agricultural, consumer manufacturing, and health care industries, particularly among Gram-negative *Enterobacteriaceae*, some of the most common community and healthcare-acquired bacterial pathogens [38]. Antibiotic resistance may occur after exposure of various Gram-negative species to sub-lethal concentrations of some biocidal agents such as benzalconium chloride, chlorhexidine or triclosan [18]. *Escherichia coli* organisms have increasingly become resistant to commonly used antimicrobial agents [21]. The ability of *E. coli* to acquire and transfer antibiotic resistance and virulence genes makes them important in both human and animal health [37].

Within the livestock sector, poultry emerges as the most efficient sub-sector in its use of natural resources and providing protein to supply a global growing demand [26]. According to the FAO statistics, poultry has become the most widely consumed meat worldwide [12]. Chicken meat could serve as a reservoir for the spread of multidrug resistance *E. coli* strains harbouring resistance and virulence genes through the food chain that could pose serious risks to human public health [5]. The plausibility of foodborne transmission of antimicrobial-resistant *E. coli* to humans is supported by the finding that antimicrobial-resistant *E. coli* from chicken carcasses widely contaminate the kitchen during meal preparation and can appear in the intestinal tract of individuals who prepare food dishes from the carcasses [23].

Fosfomycin-trometamol has a reasonable effectiveness as a last-resort oral treatment for lowering urinary tract infection and stepdown treatment for upper urinary tract infection in kidney transplant recipients [40]. Fosfomycin-trometamol could be an alternative option to carbapenems in the treatment of multidrug-resistant Enterobacterales infections for male urinary tract infections [4]. Fosfomycin have recently received research attention because of the rapid spread of multidrug-resistance [5]. The detection of mobile fosfomycin-resistant genes in *Enterobacteriaceae* has increased in recent years. Mobile fosfomycin-resistant genes have been detected in isolates of human, animal, food, and environmental origin which leads to a growing concern regarding the risk of the spread of such bacteria, especially *E. coli* at the human–animal–environment interface [47].

With an increase in the biocidal product usage, the emerging bacterial resistance is possible [22], however, due to the insufficient investigative data and the lack of standardized protocols, the full magnitude of the possible impact of biocides on AMR in the long term remains difficult to assess [36]. The scientific research on the short- and long-term impact of the wide use of biocides for environmental and personal disinfection, including cross resistance to antimicrobials were called for in a recently editorial published in the WHO Bulletin [11].

The aim of this study was to examine the influence of the overuse of disinfectants and biocides during COVID-19 emergence on the resistance in poultry meat of *E. coli* to fosfomycin. In Algeria, fosfomycin is prohibited for veterinary use [25]. So the risk of antibiotic resistance linked to its use in poultry farming is thus eliminated and the confusion bias is controlled.

This paper focuses on the increase in fosfomycin resistance of *Escherichia coli* isolated from poultry meat

that accompanied the excessive use of biocides during the COVID-19 outbreak in Algeria.

## MATERIALS AND METHODS

### Sample collection

The research took place between January 2018 and July 30, 2020, in the Algerian city of Biskra, a total of 159 diverse pieces of poultry meat samples were purchased from ten butcher shops. All samples were subjected to a bacteriological analysis. A total of 134 *E. coli* isolates were identified from poultry meat samples following the FDA's Bacteriological Analytical Manual [8]. Ninety four *E. coli* strains were isolated from poultry meat samples which were bought from the butcher's shops previous of the COVID-19 outbreak, between January 2018 to January 2020, and an additional forty *E. coli* strains were isolated from poultry meat samples which were bought from the same butcher's shops (10 shops) after the emergence of COVID-19 outbreak, between June 15, 2020 and July 30, 2020.

### Media for culture

Violet Red Bile Lactose Agar (VRBL), Triple sugar iron Agar (TSIA), Mannitol-Mobility medium, Muller-Hinton and Simmons citrate medium (Himedia, India), Nutrient agar (Bioscan, Algeria), Mac Conkey Agar and Plate Count Agar (Liofilchem, Italy). Analytical Profile Index galleries (API 20 E) (Biomerieu, France), Antibitic-disc fosfomycin 200 µg (Biomaxima, Poland), B-galactosidase disks (ONPG) and Oxidase discs (Himedia, India), were utilized for media culture.

### Bacteriological analysis

Three to six representative colonies (purple-red colonies that are 0.5 mm or larger in diameter and surrounded by a zone of precipitated bile acids) in VRBL (Violet Red Bile Lactose) agar from plates of each sample were picked on MacConkey agar and transferred each to a tube of BGLB (Brilliant Green Bile Broth with Durham Tube), according to the FDA's Bacteriological Analytical Manual (U.S. Food and Drug Administration). Bacteria from Durham tubes were evaluated for gas generation after a 24- and 48-hour incubation period at 35 °C. Gram stain was used to establish that gas production was not due to Gram-positive lactose-fermenting bacilli. Additionally, biochemical tests on positive (gas) tubes were carried out (Triple SugarIron Agar (TSIA): acid/acid; gas positive; $H_2S$ negative; citrate: negative; urease: negative; indole: positive). To confirm *E. coli*, API-20E strips were utilized.

### *E. coli* antimicrobial susceptibility testing

Fosfomycin (200 µg) susceptibility of *E. coli* strains was done with the disc diffusion method. First, a pure culture of the *E coli* is grown in *Tryptone Soya Broth:* TSB (Himedia, India). Then the bacteria solution density used is 0.5 McFarland. A sterile cotton swab is used to streak the bacterial culture evenly across the surface of a Mueller-Hinton agar plate. Fosfomycin (200 µg) disc is placed on the agar surface, gently pressing it down to ensure good contact. The agar Mueller-Hinton media with antibiotic discs were incubated at 37 °C the for 18–24 hours. After incubation, the plates are examined for the presence of clear zones around the antibiotic disks. The size of the inhibition zone is measured in millimetres from one edge of the clear zone to the other edge of the clear zone. The size of the inhibition zone is then compared to the established guidelines by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Resistant strain has the size zone of $< 24$ mm.

### Statistical analysis

Before and after the appearance of COVID-19, *E. coli* were isolated from poultry meat and compared according resistance to fosfomycin (200 µ). ANOVA test and the chi-squared test ($X^2$) were used to perform a univariable analysis. The odds ratios and 95 % confidence intervals (CI) were determined for risk factor that was statistically significant. Multivariate analysis was done with the binary logistic regression. The diagnostic value of the constructed model was examined via Nagelkerke. The various confidence intervals will be presented at the 95 % significance level and $P = 0.05$ as degree of significance. All statistical analyses were performed using SPSS software, version 21.

## RESULTS

### Effect of the COVID-19 appearance on the fosfomycin *E. coli* resistance

Fosfomycin susceptibility mean of *E. coli* isolated from poultry meats bought before COVID-19 emergence

was significantly larger than those isolated from poultry meats bought after COVID-19 pandemic (P = 0.011). Box-plots were used to check the data distribution (Fig. 1).

The frequency of fosfomycin *E. coli* resistant strains was found higher (15.56 %) after COVID-19's appearance than before COVID-19 (1.69 %) in poultry meat (Fig. 2).

Significant relationship between Fosfomycin *E. coli* resistance in poultry meat and COVID-19 appearance (Chi-square test $X^2$, P < 0.05), furthermore the effect of COVID-19 appearance on the fosfomycin *E. coli* resistance was OR = 10.68 (95 %; CI 1.26–90.34; P = 0.009).

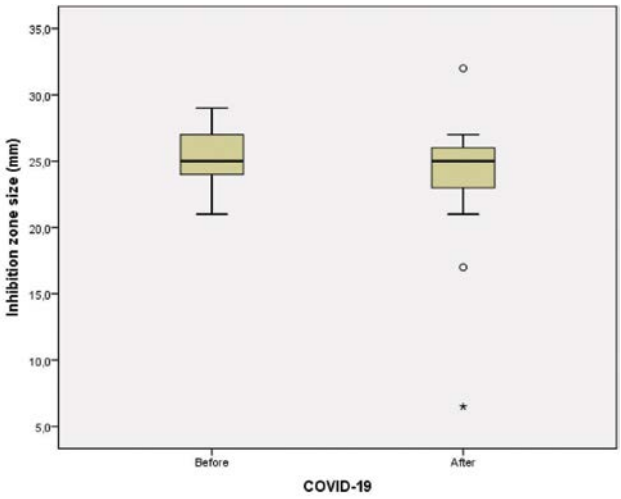



**Fig. 1. Box-plot of fosfomycin susceptibility in *E. coli*, estimated from inhibitor zone deviations**

Comparison between distributions of inhibitor diameter zone of resistance in fosfomycin of *E. coli* isolated from poultry cuts before and after the COVID-19 appearance. The box-plots indicated the median value (the line within each box) and interquartile range (the upper and lower boundaries of each box), whiskers below and above each box presented the 10th and 90th percentiles. The lower the inhibitor zone diameters are on the y-axis, the more the fosfomycin *E. coli* resistance is.

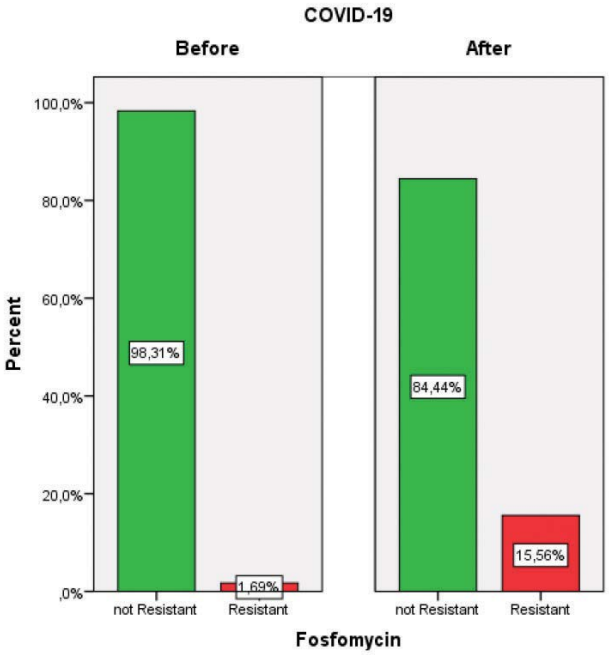



**Fig. 2. Fosfomycin resistance frequency in *E. coli* strains isolated from poultry meat before and after COVID-19**

## Independent predictor

To detect if COVID-19 emergence is an independent predictor to the fosfomycin resistance in poultry meat, binary logistic regression was done.

The logistic model was significant according to the omnibus Tests of Model Coefficients ($X^2$ = 7.37; P < 0.05). Nagelkerke $R^2$ = 0.16, suggests that the strength of association between fosfomycin *E. coli* resistance and COVID-19 emergence was 16 %.

Table 1 presents the regression coefficients of the predictors *B*, the Wald statistic, and the P values. After COVID-19 appearance (OR 10.68; 95 %; CI 1.26–90.34; P < 0.05) was observed to be significant to predict fosfomycin resistance in *E. coli* strains isolated in poultry meat (Table 1). *E. coli* strains isolated from poultry meat bought after COVID-19 emergence were 10 times more likely to be fosfomycin resistant than *E. coli* strains isolated from poultry meat bought before COVID-19. The probability of fosfomycin *E. coli* resistance associated with poultry meat purchased after COVID-19 was 2 times more than before the appearance of COVID-19.

**Table 1. Binary logistic regression analysis results**

| Equation variables | Regression coefficient B | Wald | Significance | OR | 95 % CI for OR | |
|---|---|---|---|---|---|---|
| | | | | | Lower limit | Upper limit |
| Constant | -4.06 | 16.20 | 0.001 | 0.017 | | |
| Before/After COVID-19 | 2.37 | 4.73 | 0.03 | 10.68 | 1.26 | 90.34 |

OR – odds ratio; CI – confidence interval

## DISCUSSION

This paper focused on the increase in fosfomycin resistance of *E. coli* isolated from poultry meat that accompanied the excessive use of biocides during the COVID-19 pandemic in Algeria. According to the list of medicines for veterinary use in Algeria, fosfomycin is not approved for use in poultry farming [25]. Moreover, fosfomycin does not exhibit cross-resistance with other classes of antibiotics [30]. As a result, the risk of antibiotic resistance associated with its use in chicken production is eliminated, and therefore the confusion bias is controlled.

### Fosfomycin *E. coli* resistance before COVID-19 emergence

Before the emergence of COVID-19 pandemic in Algeria, the resistance to fosfomycin of *E. coli* strains isolated between January 2018 and January 2020, from poultry meat found in this study was 1.69 % (Fig. 2). Similar results were found, overall, 7.3 % of chickens were found to be colonized by fosfomycin-resistant *E. coli* during 2008 to 2010 in Hong Kong [15]. Fosfomycin resistance was detected in 8.8 % of *E. coli* isolates from chickens [45]. Fosfomycin is not approved for use in food animals in China.

### Fosfomycin *E. coli* resistance after COVID-19 appearance

Fosfomycin *E. coli* resistance in poultry meat, found in this study, increased to 15.56 % after COVID-19 appearance (Fig. 2). Even so, fosfomycin is always not allowed for aviculture use. Thus, the high frequency of fosfomycin resistance found in this study was unexpected and was not due to the selective pressure resulting from exposure to fosfomycin [45].

*E. coli* resistance was often associated with changes in susceptibility to some antibiotics, most prominently with increased resistance to fosfomycin [17]. Fosfomycin resistance is not routinely tested in most monitoring and surveillance studies and in many studies, fosfomycin resistance is not of main interest, these might cause underestimation of the current situation of the spread of mobile fosfomycin-modifying enzymes [47]. Moreover, emerging fosfomycin resistant pathogens in poultry present potential food safety and public health risks [31]. H u a n g et al. [16] reported the emergence of a novel plasmid-mediated *fosA* gene, *fosA10*, conferring high-level *E. coli* resistance to fosfomycin collected from a chicken meat sample outlet in Pakistan in 2018 [16]. Four of the *E. coli* isolates recovered from faecal samples harboured fosfomycin resistance gene, highlighting the importance of monitoring the emergency of fosfomycin resistance [44]. The presence of plasmid mediated fosfomycin resistance genes from chicken *E. coli* isolate in Egypt [29]. Two fosfomycin-resistant FosA4, were detected in *E. coli* strains from chickens in Egypt in 2019 [39]. Recent data from food animal studies showed that limiting the use of antibiotics in food animal production resulted in modest reductions in the prevalence of resistance, instead of elimination of resistance, in certain bacteria [46].

In this study, *E. coli* isolated from poultry meat purchased after the COVID-19 appearance were more resistant to fosfomycin than those isolated before COVID-19 appearance, as mentioned in (P = 0.011) and (Fig.1). Poultry meat purchased after the emergence of COVID-19 was also associated to fosfomycin *E. coli* resistance (P = 0.009; OR = 10.68; 95 %; CI 1.26–90.34). From the logistic regression analysis we found that the *E. coli* strains isolated from poultry meat purchased after the appearance of COVID-19 are 10 times more likely to be fosfomycin resistant than *E. coli* strains isolated from poultry meat purchased before the emergence of COVID-19. The probability of fosfomycin *E. coli* resistance associated with poultry meat purchased after the emergence of COVID-19 is 2 times more than before the appearance of COVID-19 (Table 1).

This result of increase found in fosfomycin *E. coli* resistance may be explained by the fact that the overuse of biocides, during the COVID-19 outbreak, in Algeria. The Algerian government has issued several decrees laying down additional measures to prevent the spread of coronavirus, according to World Health Organization's guidance on the cleaning and disinfection of environmental surfaces in the context of COVID-19 [43]. These measures include making disinfectant products available to users and customers,

in particular hydro-alcoholic gels, and daily cleaning and disinfection of business premises [27]. Algerian authorities ordered the closure of all shops (except food stores) in all the national territory [20]. Hydroalcoholic solution was available for employees in 85 % and for customers only in 4 %. In more than 70 % of cases, disinfection of surfaces, floors and door handles took place frequently according to survey of 115 service sector companies carried out in the prefecture of Setif (Algerian city) in order to evaluate the preventive measures taken by the service sector companies against the spread of the virus [14]. The Algeria Press Service stated, on March 21, 2020, that several companies in the public and private sectors of the sanitation, disinfection and personal hygiene products sector have doubled their production capacity with the spread of the corona virus (COVID-19) in Algeria. The production capacity of the public sector companies specialized in the production of disinfectants and personal hygiene products is 1000 units/day for disinfectant gel and liquid soap, 4000 litres/day for surface cleaners as well as 4500 units of bleach. This unit should increase its production capacity to 3000 units/day of disinfectant gel and liquid soap, 20000 litres of floor cleaner as well as 10000 bottles of bleach [2].

The primary cause of AMR is the extensive use of antibiotics; furthermore, increased biocides usage will increase AMR by co-resistance [33]. The excessive use of antiseptics and biocides leads to resistance against these compounds and cross-resistance to antibiotics [42]. Merchel–Piovesan–Pereira et al [24] systematically performed adaptive laboratory evolution of the gut bacteria *E. coli* in the presence of sub-inhibitory, constant concentrations of ten widespread biocides. Their results showed that 17 out of 40 evolved strains (43 %) decreased the susceptibility to medically relevant antibiotics [26].

There is little published research about the possible role played by biocide residues (present on inanimate objects or skin) acting as a selective influence for antibiotic-resistant bacteria [35]. This is particularly pertinent with the increased usage of biocidal products and the usage conditions in animal husbandry [22]. The antibiotic resistance was highly associated with disinfectant. The farms or processing environment may be a major source for cross-contamination with *Salmonella*. Therefore, the retail meats may be a reservoir for the dissemination of antibiotic resistant *Salmonella* and using disinfectants for decontamination in live-stock may provide a pressure for co-selecting strains with acquired resistance to other antimicrobials [6]. Extensive use of antimicrobial processing aids (APA) at sub-lethal concentrations in poultry processing operations may lead to the selection of antibiotic-resistant bacteria and may represent a public health concern [32]. Biocides displayed strong selective pressures on antibiotic resistance genes exerted by intensive farming [19]. The genetic evidence presented here clearly suggests these non-antibiotic factors including biocides contribute to the maintenance of AMR in pig farming [19].

## CONCLUSIONS

Many *in vitro* studies have often resulted in reduced susceptibility to biocides and increased minimal inhibitory concentrations for antimicrobial agents. This study examined *in vivo* the effect of the excessive use of disinfectants and biocides as a means of controlling the spread of the virus during the COVID-19 pandemic on the resistance of *E. coli* to fosfomycin in poultry meat. Poultry meat purchased after COVID-19 appearance was found to be related to fosfomycin *E. coli* resistance.

### Conflict of interest

The authors declare no conflicts of interest related to this report.

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