



## Global impact of antimicrobial resistance

Raghavendra L. Girijala<sup>1</sup>, Ruth L. Bush\*<sup>2</sup>

### ABSTRACT

The advent of the first antimicrobial medication in 1928, penicillin, gave healthcare practitioners a powerful tool in their arsenal with which to combat infectious disease. Since the days of penicillin, medical technology has continued to generate scores of antimicrobial agents, targeting bacteria, fungi, viruses, and protozoa. However, these organisms have concurrently evolved mechanisms of antimicrobial resistance, and the medical community is losing an arms race with infectious organisms that were once simple to treat. Therefore, the onus is now not only on the medical community, but also the agriculture and pharmaceutical industries to address this issue promptly. This review will summarize the causes for concern, causes of increasing resistance rates, global impact, and potential strategies to prevent the end of the antimicrobial era.

### INTRODUCTION

Antimicrobial resistance (AMR) is defined as the ability of microbes to resist the effects of drugs, thereby limiting the treatment options and increase cost and potential side effects for patients.<sup>1</sup> The causative events driving resistance rates in microbes are multi-factorial, including but not limited to poverty, misuse of antimicrobials in agriculture, incorrect dosing or prescription, lack of diagnostic testing, poor surveillance, and pharmaceutical interests shifting to development of drugs for chronic illnesses. As a result, the last few decades have witnessed a rapid development of resistance in common but deadly organisms such as *S. aureus*, *K. pneumoniae*, *M. tuberculosis*, and others. To put this dilemma into context, consider that the United States, where drug resistance rates are far lower and antimicrobials are far more available than elsewhere around the globe, records over 1.7 million hospital-associated infections (HAI) per year. This results in a staggering 99,000 possibly preventable deaths and costs over \$20 billion in healthcare expenditures; these data serve to underscore the potential global impact of AMR.<sup>2</sup> However, producing more – from 1

million kilograms of medication in 1954 to current estimates of 16 million kilograms in the United States, as well as and newer antimicrobials – from penicillin to over 25 classes of antimicrobials – has not attenuated this issue.<sup>3</sup> To combat the growing problem, this review will summarize causes of concern by organism and by region, mechanisms by which resistance is being developed, the potential economic and patient impact globally, and strategies that must be undertaken to end AMR.

Due to economic constraints, case and diagnostic test availability, much of research investigating AMR rates has been based on single organisms within certain global regions. The most comprehensive surveillance report to date is from the World Health Organization (WHO) in 2014, which examined resistance rates of common infections from 114 countries.<sup>4</sup> It should be noted that no guidelines exist

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<sup>1</sup>Texas A & M University College of Medicine, College Station, TX

<sup>2</sup>Baylor College of Medicine, Houston, Texas

### \*Corresponding Author:

Ruth L. Bush

Baylor College of Medicine

Center for Innovations in Quality, Effectiveness, and Safety (IQUES)

Michael E. DeBakey Veterans Affairs Medical Center

2002 Holcombe Blvd. (152)

Houston, Texas 77030

[ruth.bush@va.gov](mailto:ruth.bush@va.gov)

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as of yet regarding methodology and data collection for a worldwide study. Therefore, surveillance in many countries has been predicated on sampling patients with severe infections, often an HAI, where first-line therapy has failed. As a result, the report likely underestimates community-acquired infections, where resistance rates may vary. Finally, data sets were often derived from individual surveillance sites or several sources, in lieu of national databases, and often had small numbers of tested isolates per bacterium. While this indicates a degree of imprecision in the findings that will be presented, it also highlights the insufficiency of global surveillance mechanisms at present.

### ANTIMICROBIAL RESISTANCE BY ORGANISM

#### *Staphylococcus aureus*

A gram-positive, beta-hemolytic, coagulase positive, catalase positive, cluster forming bacterium, *S. aureus* is both a commensal organism and opportunistic pathogen that causes a wide range of infections, including infective endocarditis, osteomyelitis, skin and soft tissue infections, secondary pneumoniae, device related infections, bacteremia, and toxic shock syndrome.<sup>5</sup> The first report of AMR in *S. aureus* was published in the 1940s, where a penicillin inactivator was extracted from 7 strains, allowing development.<sup>6</sup> This drove development of beta-lactamase inhibitors such as clavulanate and sulbactam. The combination of penicillin with beta-lactamase inhibitors augmented the ability to fight infection, until in the 1960s, when the first reports of methicillin-resistant staphylococci (MRSA) were reported; these strains, via a *mecA* gene, were able to encode an altered penicillin-binding protein.<sup>7</sup> As a result, treatment options for MRSA strains became limited to vancomycin, linezolid, and daptomycin.<sup>8-10</sup> However, according to the WHO report, non-susceptibility to vancomycin is on the rise, while MRSA resistance is over 20% in all WHO regions.<sup>4</sup>

#### *Escherichia Coli*

*E. coli* is a gram-negative, facultative anaerobic bacterium best known for its colonization of the gastrointestinal tract. It is also known to be the most frequent cause of community and hospital acquired UTI and pyelonephritis; other infections include

neonatal meningitis and foodborne infections.<sup>11</sup> Depending on the strain, *E. coli* can cause dysentery, traveler's diarrhea, and even hemolytic uremic syndrome.<sup>12</sup> Severe infections are often treated with third generation cephalosporins or fluoroquinolones, but the WHO report indicates that resistance is globally increasing.<sup>4</sup> With respect to fluoroquinolones, resistance is via gene mutation in target enzymes, while resistance to broad-spectrum penicillin and cephalosporin-based drugs resistance is attributed to mobile genetic elements encoding extended spectrum beta-lactamases (ESBL).<sup>13,14</sup> Due to the number of strains with ESBLs, carbapenams have become the only remaining treatment for the most resistance bacterium. However, a growing number of strains are now producing metallo-beta-lactamase, which encodes resistance to carbapenams as well.<sup>4,15</sup>

#### *Klebsiella pneumoniae*

*K. pneumoniae* is a gram-negative bacterium that can normally be found in the mouth, skin, and intestines, and frequently cause nosocomial infections in the immunocompromised. It is most often associated with hospital acquired urinary tract infection, pneumoniae, soft tissue infections and septicemia due to hands of hospital staff being reservoirs for the organism.<sup>16</sup> The first case of an ESBL encoding strain was reported in 1982, and resistance has only expanded since then.<sup>17</sup> According to the WHO report, there is a high rate of resistance to third generation cephalosporins, as well as carbapenams. In fact, the majority of national sources reported over 30% resistance rates against third generation cephalosporins; some reported over 60%. With respect to carbapenams, some patient groups have reported over 50% resistance rates; in these subgroups, no treatment options remain.<sup>4</sup> Resistance in this organism is primarily due to horizontal transfer of mobile genetic elements (specifically, transposons and plasmids) and chromosomal encoding of an ESBL. Intriguingly, given that *K. pneumoniae* also colonizes the intestines similar to *E. coli*, studies have demonstrated the *E. coli* ESBL acquisition may have been from this organism.<sup>18</sup>



### *Neisseria gonorrhoea*

*N. gonorrhoea* is a gram-negative diplococci known for causing sexually transmitted disease, infertility neonatal conjunctivitis, meningitis, and Fitz-Hugh-Curtis syndrome secondary to pelvic inflammatory disease.<sup>19,20</sup> Over the last few decades, AMR in gonococci has expanded to include sulfonamides, penicillin, tetracyclines, and even fluoroquinolones.<sup>21</sup> As a result, intramuscular ceftriaxone has become the mainstay of treatment. However, according to the WHO global report, reports have already begun to appear indicating failure of ceftriaxone treatment against pharyngeal gonorrhoea.<sup>22-24</sup> Given that few other drugs are in the development pipeline to treat gonorrhoea, compounded with the large number of infections per annum, growing resistance rates pose a significant threat to patient safety given the potential complications of this infection.<sup>4</sup>

### *Mycobacterium tuberculosis*

*M. tuberculosis* is a facultative intracellular, acid-fast, gram positive rod that can survive within the body's macrophages, replicating and eventually killing the cells.<sup>25</sup> Due to severe nature of untreated disease, sputum samples from patients are tested for drug resistance to determine the course of treatment. This is done by the newer Xpert MTB/RIF assay, which uses nucleic acid amplification to detect mutations that confer rifampin resistance.<sup>26</sup> This test has been endorsed by the WHO for use in TB-endemic regions. If drug resistance does not exist, patients are currently treated with rifampin, isoniazid, ethambutol, and pyrazinamide. The first case was drug resistance discovered in the 1940s in a UK randomized controlled trial, where after 3 months of streptomycin treatment.<sup>27</sup> Seven decades later, as of 2012, 20.2% of previously treated cases and 3.6% of new cases globally are multidrug resistant; furthermore, 9.6% of reported cases globally are extensively drug resistant. This is most prevalent in Eastern Europe and Central Asia in countries which have low income status.<sup>4</sup>

### *Plasmodium species*

The protozoan genus causing malaria are transmitted via the female *Anopheles* mosquito, enter the blood stream, the liver, and, ultimately, erythrocytes. Eventually, they multiply and cause hemolysis,

disrupting oxygen transport and leading to organ damage.<sup>28</sup> Malarial drugs are unique in that they have slow elimination, thereby increasing their half-life and preventing infection by susceptible parasites but allowing infection by resistant organisms. Only in the 1950s was the first case of chloroquine resistance due to spontaneous mutations documented, followed by mefloquine resistance due to increased *pfmdr1* gene copy number.<sup>4,29,30</sup> Eventually, resistance to amodiaquine, sulfadoxine-pyrimethamine occurred, leaving artemisinin as the mainstay of treatment. Now, the first cases of artemisinin resistance are also being reported.<sup>31</sup>

### *Antimicrobial Resistance by Region*

In developed countries and regions, one of the primary drivers of AMR is microbial drug exposure, which allows for selection of resistant strains. At the same time, lower-income status patients in developed countries often have enough access to order to lower cost, but potentially poorly manufactured, medication from overseas due to the cost of drug therapy. However, this is not to imply that lower-income status countries are at lower risk for antimicrobial resistance. In fact, the WHO surveillance reports indicate that poverty is also linked to increasing resistance rates, due to several selection pressures. The first is the limited supply of medications, resulting in healthcare providers being forced to prescribe partially or non-efficacious treatments. Furthermore, poorer countries are more likely to allow antimicrobial dispensing without a prescription, and often have less precise manufacturing standards. Other causes include lack of education in less affluent regions, where patients choose not to finish treatment courses in hopes of saving the medication for another incident or share medication. Finally, due to limited medical technology and increasing complexity of infection treatment, healthcare staff in developing countries have less access to diagnostic modalities. As a result, they can often resort of empiric treatment, which may be entirely ineffective or foster further resistance.<sup>32-35</sup>

### DRIVERS OF RESISTANCE

Antimicrobial resistance is most often attributed to microbial organisms that capitalize on selection



pressures and a rapid division rate to retain only resistant organisms in their population. When considered more broadly, physician overuse or inappropriate of antimicrobials is often cited as the second most common driver. However, this is a myopic viewpoint, in that it does not account for the interplay with the agriculture and pharmaceutical industries and their role in fostering increasing AMR rates.

#### *Microbial causes*

Microbial organisms are often present in large populations in an infection site. As an individual organism, they contain limited genomes that cannot survive all conditions. However, as a population, they contain a wide range of genes that can respond to various environments. Compounded with their rapid generation time, they can rapidly select for the sub-populations that can best survive when taking antimicrobials.<sup>36</sup> With respect to the specific changes in genome content, microbes utilize two primary mechanisms: spontaneous mutations in chromosomal or accessory DNA or incorporation of complete resistance genes via horizontal gene transfer (HGT).<sup>37</sup> Mutation, in individual microbes, is not an effective method to develop resistance due to low frequency of occurrence; however, due to large populations of microbes, even miniscule mutation probabilities becomes highly likely. With respect to horizontal gene transfer, this can occur via plasmids, transposons, and other similarly transposable elements containing adaptive genes. Unlike spontaneous mutation, HGT has been demonstrated to increase in response to stress; this may be due to increasing proportions of resistant organisms that participate in HGT as selection pressures persist.<sup>38</sup>

#### *Overuse or misuse*

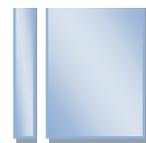
Practice patterns by healthcare providers are certainly part of the rise in AMR. One study conducted a global analysis of antibiotic consumption from 2000 to 2010 by using sales data for retail and hospital pharmacies from the IMS Health MISAD database to review use patterns in 71 countries. They found that over the decade, there was 36% increase in antimicrobial usage, which was largely attributed to lower-income countries such as India, Brazil, and China. Furthermore, there was a

marked increase in use of last-resort drugs.<sup>39</sup> While underdeveloped countries have certain pressures to drive such usage statistics, even developed countries such as the United States are contributing. According to a 2013 report by the CDC, inappropriate antimicrobials were used with respect to clinical indications, agent choice, and treatment duration in up to 30% of cases.<sup>40</sup> Considering the diagnostic modalities and treatment options available in the United States, the rates for other countries can be inferred to be even higher.

Part of the issue with misuse or overuse stems of patient demand for antimicrobials. A lack of global health literacy has been well-documented; compounded with an increasing consumer-esque nature to healthcare interactions between patient and provider, this has led to pressure on providers to prescribe medications that are not necessary.<sup>41,42</sup> Furthermore, although diagnostic testing is available, it can take time for results to arrive. As a result, practitioners may choose to empirically treat based on experience and epidemiology in their practice location. This is a double-edged sword, as a correct deduction of the pathogen shortens infection-related harm, but an incorrect guess can lead to AMR and increase treatment cost.<sup>36</sup>

#### *Agricultural use*

Human use of antimicrobials is often the primary focus in AMR discussions, but according for the 2013 World Healthcare-Associated Infections Forum, 80% of all antimicrobials are consumed by food-producing animals, in an effort to limit infections.<sup>43</sup> Due to the potential overuse of antimicrobials, four separate studies in different locations (The Netherlands, United States, and Europe) investigating *E. coli* virulence determined that related resistance genes were present in strains in humans and animals.<sup>44-47</sup> Furthermore, *E. coli* genomes in chicken meat demonstrated 79.8% prevalence of EBSL genes in The Netherlands. More importantly, the EBSL genes in chickens and humans were identical.<sup>48</sup> A larger ecologic study in Europe also demonstrated that resistance in *E. coli* isolates in poultry and pigs was similar to resistance in human isolates, further supporting evidence for cross-species strain transfer.<sup>46</sup> Most worryingly, the agricultural



consumption rate is only increasing. One study estimated that between 2010 and 2030, the global antimicrobial use in animals will increase 67%, mostly attributed to countries such as Brazil, Russia, India, China, and South Africa.<sup>49</sup>

**Research and Development**

Although antimicrobial use continues to increase, the development of new drug classes and molecules has stagnated. Due to the greater profit margins for drugs treating chronic illnesses, pharmaceutical companies have largely abandoned antibiotic development.<sup>50</sup> In fact, of 18 major global pharmaceutical firms, only 3 continue to develop antibiotics today.<sup>51</sup> As a result, after 1998, only 2 drugs with new microbial targets have been created, and no new drug classes have been made to target gram-negative bacilli over the past forty years.<sup>51</sup> In terms of research, new hope has been discovered in the form of teixobactin, a cell wall synthesis inhibitor that demonstrates no resistance development in *S. aureus* or *M. tuberculosis*, due to its multiple mechanisms of action.<sup>52</sup> However, more important than the discovery of teixobactin is the manner in which it was isolated. Previously, most antibiotic development centered on soil microbe screening, which limited the compounds discovered because most microbes cannot be grown *in vitro*. Instead, the

new method utilizes an electronic chip to culture microbes in soil and isolate the antimicrobial compounds generated.<sup>52</sup> If pharmaceutical firms coordinated with these efforts, great strides could be made to tackle AMR.

**FUTURE IMPACT**

Economically, the result of our current failure to limit AMR is predicted to reduce global population between 11 to 444 million by 2050. As a result, this annual decrease in gross domestic production could lead to a deficit of 2.1 to 124.5 trillion dollars.<sup>53</sup> However, these projections do not account for increases in healthcare direct and indirect costs. For example, patients with microbial infections resistant to empiric treatment often have increases length of stay (LOS), use of more costly and toxic treatment, and risk of complications.<sup>54</sup> Due to nature of the hospital, this further increases risk of resistant infections and death. Specifically, antibiotic resistant infections prolong LOS by 6.4 to 12.7 days, totaling to 8 million extra hospital days.<sup>55</sup> Economically, this equates to 20 billion dollars in direct costs, and over 35 billion in indirect costs.<sup>55</sup> Given that the aforementioned costs are limited to just the United States, the scope of AMR to the global economy cannot be understated.

Organism	Resistant to	All-cause mortality	Bacterium-attributable mortality	30-day mortality	Length of stay (LOS)	ICU admission	Postinfection LOS in hospital	Progression to septic shock
E. coli	Cephalosporin	2.18 [158, 3.02] p < 0.00001 18	2.02 [141, 2.90] p < 0.0001 4	2.18 [178, 2.68] p < 0.00001 11	No significant increase [-13, 5.0] p = 0.25 4	No significant increase [-58, 13.20] p = 0.20 1	No significant increase [0.25, 4.90] p = 0.08 4	
	Fluoroquinolone	2.11 [164, 3.71] p < 0.00001 8	No significant increase 1 study used	RR = 2.16 [109, 4.27] p = 0.03 5	No significant increase [3.49, 10.94] p = 0.31 2	2.40 [1.08, 5.35] p = 0.03 1		10.00 [1.19, 84.36] p = 0.03 2
K. pneumoniae	Third generation cephalosporins	1.35 [114, 1.61] p = 0.0007 14	1.33 [1.13, 3.31] p = 0.02 4	1.45 [1.07, 1.95] p = 0.02 7	No significant increase [2.6, 34.2] p = 0.09 9	1.39 [1.08, 1.80] p = 0.01 3		No significant increase [0.64, 1.53] p = 0.97 3
	Carbapenam	1.71 [1.35, 2.18] p < 0.0001 11	No significant increase [.61, 6.43] p = 0.25 1	1.51 [1.19, 1.91] p < 0.0006 3	No significant increase [-11.9, 13.8] p = 0.88 2		No significant increase [-21.7, 31.7] p = 0.71 1	
S. aureus	Methicillin	1.61 [1.43, 1.82] p < 0.00001 107	1.64 [1.43, 1.87] p < 0.00001 46	1.59 [1.33, 1.91] p < 0.00001 16	Mean diff = 4.65 [2.96, 6.33] p < 0.00001 50	1.07 [0.92, 1.25] p = 0.36 17	Mean diff = 3.12 [1.79, 4.44] p < 0.00001 27	1.52 [1.24, 1.88] p < 0.0001 21

RR  
[ ]  
p value  
# studies used  
Unless otherwise indicated, organized as follows

**Fig 1 Health Impact Based on Microbial Organism and Drug Resistance**  
Green indicates significant correlation; gray indicates no significant change; black indicates no data available.



With respect to patient outcomes, measures such as 30-day mortality, intensive-care mortality, LOS, progression to septic shock are usually measured by individual studies by organism. The most comprehensive report on such measures is the WHO 2014 surveillance report, which collated hundreds of studies to determine clinical outcome based on microbial organism and resistance.<sup>4</sup> However, there are limitations to this data set, as the majority of these studies were conducted in upper or middle income status countries, due to the lack of resources in lower-income regions. Furthermore, the data sets outside of the organisms represented in figure 1 are limited. Nevertheless, the results are striking, indicating that infections with resistant microbes significantly worsen many key clinical outcomes in patients.<sup>4</sup>

#### PREVENTION

A multi-factorial approach must be taken to counteract the rising rates of AMR, ranging from preventing microbial transmission, changes in waste disposal and agricultural antimicrobial use, stewardship programs, and development of new drugs and diagnostic tests. This is by no means a comprehensive list, but does encompass the most effective or necessary strategies based on the current landscape.

##### *Hand hygiene*

Hygienic handwashing is the single most effective, simple, and cheapest method to prevent infection.<sup>56</sup> By decreasing infection rates, less treatment is required, decreasing microbial exposure to our existing arsenal of drugs, resulting in less opportunity to develop resistance. Currently, a variety of compounds are used for hand hygiene, including plain soap, alcohols, quaternary ammonium compounds, chlorhexidine, and other agents. These agents, as a group, are broadly effective against the majority of microbial organisms, but have limited activity against spore-forming agents.<sup>57</sup> Historically though, the issue is not with compound efficacy but with non-adherence. To combat this, future guidelines and policies in healthcare settings must implement measures to reduce time needed to wash hands, place accessible reminders for staff to wash

hands, keep antiseptic by the bedside, and other measures that make handwashing part of the routine in the day, not a separate task that needs to be completed.<sup>58,59</sup>

##### *Biomedical waste disposal*

Biomedical waste is a known reservoir of infectious pathogens and multi-drug resistant (MDR) microbes. As such, improper waste management increasing the risk of transmitting pathogens from healthcare environments to the community. For example, one study conducted in Nigeria analyzed collected hospital waste for antibiotic susceptibility patterns demonstrated high rates of MDR *S. aureus*, *E. coli*, and other microbes.<sup>60</sup> Another study in Nepal similarly demonstrated that healthcare waste products contained MDR pathogens.<sup>61</sup> Interestingly, many of the studies conducted regarding biochemical waste disposal and its contribution to AMR arise from lower-income countries, indicating the need to implement proper mechanisms to separate, store, handle, treat and dispose waste.<sup>62</sup>

##### *Agricultural usage*

Given that the agricultural industry continues to increase antimicrobial use, the US Food and Drug Administration (FDA), CDC, and Department of Agriculture have all released statements indicating the link between use in food animals and AMR.<sup>63</sup> Moving further in the right direction, in 2012, the FDA has begun to ban use of cephalosporins in certain animals, going as far as to state that they find "the most significant risk to public health associated with antimicrobial resistance to be antimicrobial-resistant bacteria resulting from the exposure of food producing animals to antimicrobials."<sup>64</sup> Following the example being set by the FDA, other government agencies must begin to draw and enforce policies that limit antimicrobial use. Given that the food industry can be expected to focus on their profit margins and growth, government regulation is needed globally to stymie this driver of AMR.

##### *Antibiotic stewardship programs*

Given the broad set of steps required to reduce AMR rates in healthcare settings, antibiotic stewardship programs have been implemented, with the goal



being to reduce treatment cost and resistance rates.<sup>65</sup> The programs focus primarily on education, with front end and back end interventions. With respect to front end measures, these include developing situation-specific treatment guidelines and educating prescribers on them, using diagnostic techniques to measure antimicrobial susceptibility prior to treatment, and restricting the formulary and requiring preauthorization.<sup>66</sup> The latter, according to the Infectious Disease Society of America (IDSA) and Society of Healthcare Epidemiology of America (SHEA), is the most vital aspect of front end interventions.<sup>67</sup> In contrast, back-end interventions focus on reviewing empirical therapy use and discontinue treatment based on susceptibility testing, conducting post-prescription review, and employing antibiotic heterogeneity (cycling or mixing antibiotics). Although the latter is debated, the review and feedback on prescriptions after 48 to 72 hours is key to the IDSA and SHEA strategy.<sup>67</sup> While these programs require significant resources to implement, it is likely that many hospitals worldwide would be able to implement some aspects in order to reduce practitioner related drivers in AMR.

#### *Diagnostic testing and drug development*

Unlike in decades prior, broad-spectrum empiric treatment is no longer an option in our medical landscape. As such, there is an impetus for development of diagnostic techniques to allow us to leverage narrower spectrum antimicrobials. This serves a dual purpose, to reduce AMR and also maintain the normal microbiota, which can aid in protecting niches against pathogens.<sup>68</sup> Finally, as discussed prior with teixobactin and the pharmaceutical industry, drug development needs to start reprioritizing antimicrobial development. When they do, focus can be placed on screening antibiotics *in vitro* under host-like conditions or pursuing drugs with synthetic lethality.<sup>68</sup> Some studies, though, indicate that the future of antimicrobial development may lie with using metagenomics to sequence populations of bacteria; this allows avoidance of culturing and elucidation of novel biosynthetic pathways.<sup>69</sup> Regardless of the approach, it is evident that restarting the drug pipeline is a key element in combating AMR.

#### CONCLUSION

The prognosis in our fight against antimicrobial resistance is not bright at the current moment. Lack of medical resources, education, compliance, and many other factors discussed here are contributing to what will soon be a global crisis. Nevertheless, there remains a significant window of time in which we can prevent this post-antimicrobial era. This will require coordination between global medical, pharmaceutical, agricultural, and even government organizations, as nothing less than a coordinated effort will overcome this matter.

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