Antimicrobial resistance: a global response*

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Abstract Resistance to antimicrobial therapies reduces the effectiveness of these drugs, leading to increased morbidity, mortality, and health care expenditure. Because globalization increases the vulnerability of any country to diseases occurring in other countries, resistance presents a major threat to global public health, and no country acting on its own can adequately protect the health of its population against it. International collective action is therefore essential. Nevertheless, responsibility for health remains predominantly national. Consequently, there is a potentially significant disparity between the problems and solutions related to antimicrobial resistance and the institutions and mechanisms that are available to deal with them.

This paper considers the capacity of national and international institutions and mechanisms to generate a collective response to antimicrobial resistance. Strategies for containing resistance are outlined, with particular reference to globally coordinated activities of countries. The adequacy of national and international responses to resistance is assessed, and the actions that international bodies could take to solve difficulties associated with present responses are highlighted. Approaches are suggested for securing international collective action for the containment of antimicrobial resistance.

Keywords Drug resistance, Microbial; Anti-infective agents; Drug utilization; Drug and narcotic control; Research; International cooperation (*source: MeSH, NLM*).

Mots clés Résistance microbienne aux médicaments; Antiinfectieux; Utilisation médicament; Contrôle drogues et stupéfiants; Recherche; Coopération internationale (*source: MeSH, INSERM*).

Palabras clave Resistencia microbiana a las drogas; Agentes antiinfecciosos; Utilización de medicamentos; Control de medicamentos y narcóticos; Investigación; Cooperación internacional (*fuente: DeCS, BIREME*).

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Introduction

The ability of microorganisms to become resistant to the major therapies used against them has long been recognized and is becoming increasingly apparent (*1*, *2*). Resistance rates for many isolates are rising but are highly variable. For example, the proportion of isolates of *Staphylcoccus aureus* resistant to methicillin increased from close to zero 10–15 years ago to approximately 70% in Japan and the Republic of Korea, 40% in Belgium, 30% in the United Kingdom, and 28% in the USA by 1998 (*1*). Recent rates of resistance to *Streptococcus pneumoniae* were less than 2% in Belgium, Italy, and Finland, but 7% in Germany, 9.5% in Iceland, 25% in Romania, 44% in Spain and 58% in Hungary (*3*).

Increasing antimicrobial resistance (AMR) presents a major threat to public health because it reduces the effectiveness of antimicrobial treatment, leading to increased morbidity, mortality, and health care expenditure (*4*). For example, the mortality rate in outbreaks involving resistant strains of *Salmonella* spp. was found to be 3.4%, whereas it was only 0.2% in those involving sensitive strains (*5*). In 1995 the cost of containing an outbreak of infection caused by methicillin-resistant *S. aureus* in a district general hospital in the United Kingdom was estimated to exceed US$ 560 000 (*6*), while the annual health care cost associated with the treatment of resistant infections in the USA was estimated at over US$ 4 billion (*7*), an amount recently revised to more than US$ 7 billion (*8*). AMR is the cause of professional, governmental, and public concern (*9*–*12*) and has been classified as a national security risk in the USA (*13*, *14*).

The rate of development of AMR is accelerated by the use and misuse of antimicrobials (*15*). The factors responsible include over-the-counter availability of antimicrobials without professional controls (*16*), the use of drugs of low potency and effectiveness as a result of poor manufacture (*17*) or counterfeiting (*18*), and the availability of drugs from roadside stalls and hawkers who have little or no knowledge of dosage regimens, indications or contraindications (*19*). Containment of AMR thus requires a range of strategies.

AMR is a global problem (*20*). Globalization increases the vulnerability of countries to imported diseases, and infectious diseases travel faster and further than ever before (*21*, *22*). During the 1990s, for example, a resistant *Pneumococcus* sp. first identified in Spain was rapidly found in Argentina, Brazil, Chile, China (Province of Taiwan), Columbia, Malaysia, Mexico, the Philippines, Republic of Korea, South Africa, Thailand, USA, and Uruguay (*23*). No country acting on its own can adequately protect the health of its population against AMR. International collective action is essential, yet responsibility for health remains predominantly national (*24*). Consequently, there is a potentially

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significant disparity between the problems and solutions associated with AMR and the institutions and mechanisms available to deal with them (*25*).

The present paper discusses the capacity of national and international institutions and mechanisms to generate a collective response to AMR. Strategies are outlined for containing such resistance, with particular reference to globally coordinated activities. The adequacy of existing national and international responses is assessed; actions that international bodies could take in order to tackle some difficulties are examined; and approaches are suggested for securing international collective action for the containment of AMR.

Strategies for containment of antimicrobial resistance: global collective action

The eradication of AMR is neither a realistic nor a desirable goal. To eradicate resistance would require a significant reduction in the use of antimicrobials and in the benefits obtained from them. The aim should therefore be to *contain* resistance, to optimize the balance between the effective use of antimicrobials against infection, thus reducing morbidity, mortality and further spread of infection now, and the emergence and spread of resistance to the drugs leading to increased morbidity and mortality in the future.

The containment of resistance may be defined as a public good since it is impossible to exclude people from benefiting from containment, and one person who benefits does not stop another from benefiting, i.e. there is non-rivalry in consumption (*26*). These characteristics mean that the containment of resistance is bound to be suboptimal in the absence of interventions because some people rely on containment provided by others. It is important to note that the containment of AMR has these characteristics at both the global and national levels. Containment is therefore a global public good (*26*).

There are many strategies for containing AMR and these can be pursued at different levels. An illustrative list is provided in Table 1. Some strategies aim to avoid the *emergence* of new resistance, whereas others seek to prevent the *transmission* of existing resistance (*27*). Clearly, transmission can only occur once resistance has emerged. The primary goal is therefore to avoid the emergence of resistance (*28*).

Table 1 also indicates the level at which intervention is required to optimize AMR containment. Many strategies are best provided at the national level because of the diverse contexts in which policies have to be implemented and the variation in resistance to, and therefore effectiveness of, infective agents, even across relatively small areas and with the passage of time. For some strategies, however, AMR containment can clearly be achieved more efficiently by international collective action than by nations acting individually.

The dominant strategies nationally, regionally and globally are as follows: surveillance of AMR and the tracking of antimicrobial consumption; use of mechanisms to encourage research on and development of new antimicrobials and alternative treatments; and adoption of measures ensuring appropriate and rational use of existing antimicrobials (*15*).

Surveillance

Surveillance is fundamental to any strategy for AMR containment, providing the data required to locate an AMR problem, monitor its growth, transmission and direction of travel, and determine the impact of interventions intended to contain it (*15*). Collective action is required in order to produce effective surveillance systems because: the barriers to establishing surveillance systems are high, particularly for poorer nations, given the large initial investment required; surveillance produces benefits for other countries which an individual nation does not account for in deciding whether to invest in a surveillance system; and a global system requires comparable data of adequate quality.

Although there have been some developments globally, e.g. surveillance of multidrug-resistant tuberculosis (MDR-TB) (*29*), surveillance is largely undertaken in a piecemeal fashion. Few countries have well-established national networks; many microbiology laboratory facilities and information networks require strengthening; and there are no international regulations enforcing comparable collection, classification, or reporting of data. There is thus a lack of information-sharing and an incentive to obtain and use information generated by and for other countries without incurring the cost of reciprocation.

Evidence from other areas suggests that even the creation of a legal duty does not ensure compliance, but rather that compliance depends on the availability of adequate resources (*30*, *31*). Such resources are often lacking in poorer countries or subject to more extreme "opportunity costs" in terms of benefits forgone arising from the alternative use of resources for tackling health problems directly (*32*). The cost of establishing surveillance systems varies with the infrastructures and surveillance facilities that are available. Initial work on the feasibility of establishing surveillance systems globally could therefore be based on experience already gained in national surveillance to determine the level of resources required, the extent to which these are already met in particular countries, and the resources needed to set up surveillance systems at particular levels in different countries.

Research and development on new antimicrobial and other therapies

Although knowledge is a classic public good, in practice the enormous cost of research and development means that patents are used to transform it into a private good, i.e. one from which people can be excluded, thus providing the incentive for private sector investment. A key element in the future development of therapies that have lower rates of AMR, or alternatives to antimicrobial therapy, is thus to encourage research and development in the private sector.

The need for collective action in securing private sector investment primarily arises because of conflict between strategies for controlling the use of antimicrobials as a means of containing resistance and those for maintaining research and development on new antimicrobials. This is most obvious where strategies seek to restrict or reduce antimicrobial consumption, i.e. most strategies for containing the emergence of resistance (Table 1), since this threatens profitability, a function of volume and price, indicating that research and development are not likely to be undertaken. These problems could be tackled through compensating policies that might involve allowing or subsidizing increases in price to offset reduced sales volumes, considering orphan drug status for some products, or conducting advance purchase deals in order to secure an incentive for investment (*33*). Alternatively, AMR may present a market potential: by reducing the effectiveness

Table 1. **Characteristics of strategies for containing emergence and transmission of resistance**[a]

General strategies applicable to containment of both emergence and transmission of resistance	Level of intervention			
	Local	**National**	**Regional**	**Global**
1. Surveillance	Required at all levels in order to obtain an accurate picture of emerging resistances and the rate of transmission of new resistances, and to identify the impact of interventions designed to contain antimicrobial resistance in particular contexts			
2. Financial incentives or disincentives	Could be used at all levels in conjunction with many other policies as a mechanism for improving uptake of or compliance with any intervention. Would include such mechanisms as financial benefits, environmental taxes and use of permit systems			
Strategies for containing emergence of resistance				
1. Education of professionals on appropriate clinical indications	On specific problematic microorganisms in local areas	On issues most relevant to general national conditions	On general principles through regional organizations and the Internet	On general principles through global organizations and the Internet
2. Education of patients on inappropriate use and importance of compliance with instructions on taking antimicrobials	Local campaigns and ad hoc education by health professionals at time of patient consultation	By providing national information campaigns, e.g. as recently conducted in the United Kingdom (leaflets, magazine ads, etc)	On general principles through regional organizations and the Internet	On general principles through global organizations and the Internet
3. Rapid diagnosis of bacterial infections	By improving local facilities	By providing infrastructure for improved local facilities	Through provision of aid to countries whose infrastructure is lacking	Through provision of aid to countries whose infrastructure is lacking
4. Control of sensitivity data related to prescribers	From local facilities	By providing infrastructure for improved local facilities		
5. Antimicrobial policies	Developed by local facilities taking account of specific local conditions	Developed by national medical associations taking account of general national conditions		
6. Restriction of drug availability	Taking account of specific local issues BUT may potentially be considered unacceptable on grounds of geographical equity	Developed by national policy-makers taking account of general national conditions		
7. Antimicrobial cycling	Carried out at local level, taking account of prevailing local conditions			
8. Regulation of use of antimicrobials in agriculture		Developed by national policy-makers taking account of general national conditions	Through regional agreements, e.g. through the European Union	Through international agreements, e.g. through WHO
9. Choosing optimal agent, dose and dosage frequency for different infections	Carried out at patient level, taking account of prevailing local conditions and particular patient characteristics			
10. Removal of potential septic foci/prostheses	Carried out at patient level			
11. Use of drug combinations	At local/patient level, taking account of prevailing local conditions and particular patient characteristics			
12. Using antiseptics as an alternative to antimicrobials	At patient level, taking account of prevailing local conditions and particular patient characteristics	Guidelines suggesting use of alternative agents could be produced at national level		
13. Using cranberry juice as an alternative to antibiotics for urinary tract infection	At patient level, taking account of prevailing local conditions and particular patient characteristics	Guidelines suggesting use of alternative agents could be produced at national level		

Table 1, continued on p. 129

(Table 1, continued)

General strategies applicable to containment of both emergence and transmission of resistance	Level of intervention			
	Local	National	Regional	Global
14. Using probiotics as an alternative to antimicrobials	At patient level, taking account of prevailing local conditions and particular patient characteristics	Guidelines suggesting use of alternative agents could be produced at national level		
15. Increasing vaccination in order to increase immune competence	Operation of national policies at local level	National policy development concerning vaccination, including both guidance and financial incentives	Through provision of aid in order to improve vaccination levels in countries that cannot afford vaccination programmes	Through provision of aid in order to improve vaccination levels in countries that cannot afford vaccination programmes
16. Improving nutrition in order to increase immune competence	Local policy development focusing on particular communities	National policy development	Through provision of aid to countries with poor nutrition	Through provision of aid to countries with poor nutrition
17. Minimizing time patient is immunocompromised	At patient level			
Strategies for containing transmission of resistance				
1. More rapid diagnostic techniques	By improving local facilities	By providing infrastructure for improved local facilities	Through provision of aid to countries whose infrastructure is lacking	Through provision of aid to countries whose infrastructure is lacking
2. Screening of patients/ staff	E.g. on admission to hospital	Guidelines on screening could be produced at national level		
3. Use of antimicrobials to reduce infectivity	In particular patients			
4. Isolation	Of particular patients	Guidelines on isolation could be produced at national level		
5. Handwashing	In particular institutional settings	Guidelines on handwashing could be produced at national level		
6. Improvements in bed spacing	In particular institutional settings	Guidelines on bed spacing could be produced at national level		
7. Improving immunity by vaccination in order to reduce susceptibility to infection	Operation of national policies at local level	National policy development on vaccination, including both guidance and financial incentives	Through provision of aid in order to improve vaccination levels in countries that cannot afford vaccination programmes	Through provision of aid in order to improve vaccination levels in countries that cannot afford vaccination programmes
8. Improving nutrition in order to reduce susceptibility to infection	Local policy development focusing on particular communities	National policy development	Through provision of aid to countries with poor nutrition	Through provision of aid to countries with poor nutrition

[a] Heavily shaded cell = a strategy inappropriate at a particular level. Lightly shaded cell = an intervention primarily at the local or national level but which may need international aid in order to provide the intervention in some countries.

of existing drugs it may provide an expanding market for new effective drugs. In this case, AMR may itself provide an incentive for companies to invest in antimicrobials, although in practice there has been little recent development of new antimicrobials to support this.

International differences in pricing structures, patent laws, intellectual property rights legislation, and drug registration and licensing mean that companies may engage in differential research and development policies. For example, they may target the development of drugs that focus on the problems of wealthier countries (*22*, *30*). Such differentiation implies that successful policies for containing AMR in one country may simply shift the problem to another.

Collective action on a number of fronts is therefore necessary, including the reform of international patent laws and the coordination of licensing and regulatory requirements (*24*). It also includes directly undertaking or sponsoring research and development. There are precedents for international support of research and development on diseases posing significant international concern. For example, with the support of WHO and the World Bank, the Multilateral Initiative on Malaria coordinates research on antimalarial

products (*34–37*) and a similar approach should be considered also for research into new antimicrobials.

Encouraging appropriate and rational use of antimicrobials

Policies and regulations that encourage more appropriate and rational use of antimicrobials are key long-term interventions for the containment of AMR (*15*, *26*). However, the effects of many national policies may not be optimal from a global perspective if countries fail to take account of the cross-border effects of their actions. Since the sum of actions by individual nations does not equal the optimal global response, some element of collective action is therefore required. Even at the national level there are formidable problems in regulating the use of antimicrobials because of the heterogeneity of patients (the monitoring of clinical practice involves potentially high transaction costs associated with bureaucracy) and the potential conflict with clinical freedom (*38*). There is therefore a place for the use of financial incentives and disincentives at the global level, as well as for international legislation that encourages the optimal use of antimicrobials.

Little action is taking place internationally to tackle drug usage. For example, current talks between the European Union, Japan and the USA on the harmonization of pharmaceutical regulatory systems are somewhat limited, and the extent to which AMR is being specifically discussed is unclear. The potential for financial incentives and disincentives at this level has received little consideration. This is also true of the role of international legislation on enforcing strategies, covering, for example, intellectual property rights, the requirement for AMR data in the pre-approval evaluation of drugs, the use of subtherapeutic doses as growth promoters in animals, the labelling of drugs, and prescription requirements. However, work has been carried out to develop international standard treatment guidelines, which are similar, for example, to current WHO AMR surveillance standards (*39*), WHO guidelines for the treatment of MDR-TB (*40*), and WHO protocols for the detection of drug-resistant malaria (*41*). Such guidelines are important global public goods, if accessible, adaptable to local circumstances and, crucially, backed up with access to technology and infrastructure and, potentially, some form of incentive mechanism.

Securing global collective action: role of international bodies

Global collective action is clearly necessary to secure internationally compatible surveillance systems, develop new therapies, and ensure more rational use of antimicrobials. In securing collective action it is essential to consider the economic and legal dimensions, which are interrelated.

Economic dimension

Successful collective action requires the participants to perceive a net benefit, often in economic terms (*42*). This simple requirement is often overlooked. For example, whereas reductions in the use of chlorofluorocarbons were achieved relatively quickly and easily, reducing carbon emissions has been more difficult, largely because of the respective benefits and costs perceived by the USA.

Also, the imbalance of wealth between countries exacerbates the potential for "free riding", since the marginal opportunity cost of using a resource is higher in poor than wealthy nations, creating a disparity between national priorities and the place of AMR containment within them; and even if countries could be persuaded to become involved in strategies such as surveillance, many lack the financial, technical or physical infrastructure necessary to do so (*43*, *44*).

Legal dimension

A global response to AMR may be achieved through harmonization of individual national mechanisms, legislation and strategies, or through the construction of new international mechanisms, legislation, and bodies. WHO, the World Bank and the United Nations are the international organizations most qualified to take major roles in tackling these issues. Indeed, WHO has already begun to do so, with the development of its global strategy to contain AMR (*15*). However, this strategy follows the historical preference of WHO and other international bodies for operating through recommendations and guidelines, relying largely on *ad hoc* harmonization of individual national mechanisms, legislation and strategies, rather than on formal international legislation. Unfortunately, evidence suggests that this may be inadequate to contain AMR in the long run (*24*, *45*).

It may be more productive to appeal directly to international legislative frameworks, with legally binding support from wealthy nations and technical assistance and support in specific areas such as information technology. For example, international legal frameworks could cover the availability of specific drugs and labelling and licensing requirements, and would be built on agreed international legislation.

Combining the economic and legal dimensions

In order to achieve an integrated strategy encompassing global surveillance, research and development, and the more appropriate use of therapies, a hypothetical global government would ideally establish a legal imperative to comply with strategies and develop structures enabling the transfer of resources from wealthy to poor nations so that compliance could occur. In the absence of a global government, international agencies should undertake this task in order to secure international collective action.

Funding is critical. So-called "soft law", e.g. recommendations, framework conventions, and agreements, works only if countries are both willing and able to comply. For many countries the ability to comply is lacking. For example, surveillance requires procedures for collecting and transporting samples, the existence of laboratory facilities, the ability to report findings, and the monitoring of procedures and findings in diverse settings. Similarly, rational drug use requires a public health infrastructure and finance sufficient for the purchase and dissemination of good quality drugs, as well as other means of combating AMR, such as vaccination and education. This is feasible, for example, in the European Union and North America, but countries with comparatively limited resources are unlikely to be able to sustain such complex systems, with the result that the problem posed by AMR increases.

Lessons on this matter may be learnt from environmental law and economics. For example, the United Nations Convention on Biodiversity specifies the financial and technical assistance required by developing countries from

developed countries in order to reduce unsustainable development, and establishes institutional machinery for overseeing the implementation (*46*, *47*). A similar arrangement, whereby developed countries provide financial and technical assistance to developing countries or are subject to differential duties, is found within the framework protocols relating to ozone depletion and global warming (e.g. the Montreal and Kyoto Protocols). Such bargains could also be envisaged in relation to global strategies for the containment of AMR.

It is also important to consider the global funding of *access goods*, i.e. private goods required to facilitate access to the public good. For example, in order to benefit from the public good of clean water a household has to be connected to the infrastructure. Access goods, while not global public goods in themselves, may be treated as such to the extent that the international coordination of their finance and provision would lead to a more optimal outcome than if each country acted independently (*48*). They may therefore be considered to be as important as the global public good itself, for without the goods to enable the mechanisms to be utilized or to allow the benefits to be accessed the global public good of AMR containment would be difficult, if not impossible, to achieve.

A significant benefit of the concept of global public goods therefore lies in establishing the impact of a given country's non-concordance with the rest of the world community. These other nations can then be persuaded of the rationality of ensuring that the country is assisted with finance for and/or the provision of the strategy in question. To this extent, international support to strengthen national health provider systems may be seen as an important input to the containment of AMR.

Conclusion

A global approach to containment

The global nature of AMR calls for a global response. The following key activities should be undertaken by international bodies in order to encourage and promote international collective action.

Raising the profile and priority of AMR in countries. In order to secure international cooperation it is necessary to obtain national recognition of the problem that AMR presents, the interdependence of countries, and the impact and responsibility that each country has in relation to global health. This is a prerequisite for effective global collective action.

Establishment and maintenance of global AMR surveillance data to which countries contribute and have access. An important first step is the specification and coordination of international standards in laboratory susceptibility testing techniques.

Promoting standardization of research methods, coordinating research activities and disseminating information. International agencies could act as repositories for information from countries on current research projects and on the implementation and evaluation of strategies for tackling AMR. They could also assist in maintaining communication channels so as to reduce the potential for the "prisoner's dilemma" (lack of communication and information about each participant's actions, and lack of enforcement mechanisms, impeding co-operation) arising in communications between countries.

The containment of AMR is a complex process requiring action ranging from the local to the global level. The greatest problems associated with AMR undoubtedly remain to be seen. It is necessary to persuade decision-makers at the national and international levels of the importance of AMR relative to other pressing health and non-health priorities. Only if adequate strategies of collective action are implemented soon is it likely that high future morbidity and mortality attributable to AMR can be averted in all countries. ■

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Résumé

Résistance aux antimicrobiens : riposte mondiale

La résistance aux traitements antimicrobiens réduit leur efficacité et entraîne une augmentation de la morbidité, de la mortalité et des dépenses de santé. Comme la mondialisation rend les pays plus vulnérables aux maladies qui surviennent dans d'autres pays, la résistance aux antimicrobiens représente partout une grave menace pour la santé publique et aucun pays ne peut à lui seul protéger la santé de sa population contre ce risque. Une action collective internationale est donc indispensable. Mais, comme la responsabilité en matière de santé publique incombe presque toujours aux autorités nationales, il existe une disparité potentiellement importante entre les problèmes liés à la résistance aux antimicrobiens – et leurs solutions – et les institutions et mécanismes disponibles pour y faire face.

Le présent article examine la capacité des institutions et mécanismes nationaux et internationaux à organiser une riposte collective à la résistance aux antimicrobiens. Il décrit des stratégies d'endiguement, en citant particulièrement les activités des pays coordonnées au niveau mondial, évalue l'adéquation des ripostes nationales et internationales à la résistance et souligne les mesures qui pourraient être prises par les organismes internationaux pour résoudre les difficultés associées aux mécanismes actuels. Diverses approches sont proposées pour assurer que des mesures collectives puissent être prises au niveau international dans le but d'endiguer la résistance aux antimicrobiens.

Resumen

Resistencia a los antimicrobianos: una respuesta mundial

La resistencia a los tratamientos con antimicrobianos reduce la eficacia de estos medicamentos y da lugar a un aumento de la morbilidad, de la mortalidad y del gasto sanitario. Puesto que la globalización aumenta la vulnerabilidad de cualquier país a enfermedades que se dan en otros países, esa resistencia supone una grave amenaza para la salud pública mundial, y ningún país que actúe por sí solo podrá proteger adecuadamente contra ella la salud de su población. Así pues, la acción colectiva internacional es fundamental. No obstante, la responsabilidad de preservar la salud sigue incumbiendo ante todo a las autoridades nacionales. En consecuencia, se advierte una divergencia potencialmente importante entre los problemas y soluciones relacionados con la resistencia a los antimicrobianos y las instituciones y los mecanismos disponibles para abordarlos.

En este artículo se analiza la capacidad de las instituciones y los mecanismos nacionales e internacionales para articular una respuesta colectiva a la resistencia a los antimicrobianos. Se esbozan las estrategias orientadas a contenerla, y se hace especial referencia a las actividades de los países coordinadas a nivel mundial. Se evalúa la idoneidad de las respuestas nacionales e internacionales a esa resistencia, y se ponen de relieve las medidas que los órganos internacionales podrían adoptar para resolver las dificultades que plantean las actuales respuestas. Se proponen diversas alternativas para asegurar que se emprenda una acción colectiva internacional encaminada a frenar la resistencia a los antimicrobianos.

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