

Recent developments in the epidemiology and management of tuberculosis – new solutions to old problems?

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Abstract: Tuberculosis is an ancient human disease that is still a major cause of death and one of the most challenging public health problems worldwide. After decades of stagnancy, new public-private partnerships to fight the disease and the increasing awareness of a vicious circle between the tuberculosis epidemic and the obstruction of economic development have fuelled recent progress in our understanding of the disease. As a result, new strategies to improve management and treatment of tuberculosis have been initiated. At the same time, however, the devastating effect of human immunodeficiency virus on tuberculosis susceptibility and the rapid expansion of multidrug-resistant (MDR) tuberculosis threaten to undermine the advances made by tuberculosis management programs. With an estimated 9 million new cases annually, tuberculosis affects a higher number of individuals worldwide than ever before. Here, recent developments in the epidemiology and management of tuberculosis are summarized and an overview is provided of emerging strategies to combat this ancient scourge.

Keywords: tuberculosis, epidemiology, management, multidrug resistance, vaccine

Introduction

Tuberculosis is the cause of almost 2 million deaths per year. Two billion individuals, about one-third of the total human population, are infected with the causative agent of tuberculosis, *Mycobacterium tuberculosis*.¹ The great majority of infected individuals, however, are latently infected – that is, the pathogen persists in them in its dormant form. In Western countries, the disease is mostly held in check by efficient health care systems. In many regions of the developing world, however, the number of infected individuals often exceeds the capacities to provide sufficient prevention and treatment of the disease. Until the end of the last century, the rapid increase in tuberculosis prevalence in these countries was linked to a deterioration in socioeconomic development.

With the United Nations Millennium Development Goals and the Stop Tuberculosis Partnership, the World Health Organization (WHO) defined the strategy for the years to 2015 and 2050, respectively.^{2,3} The Millennium Development Goals include the halt of disease spread, efforts to reduce the incidence of disease, the reduction of death rates, as well as the improvement of detection and cure. By 2050, the aim is to eliminate the disease by reducing the global incidence to below one tuberculosis case per million individuals per year.^{4,5}

In this review, the current state of tuberculosis diagnostics and treatment, new challenges in tuberculosis control, and some of the novel approaches that are underway to improve current methods for disease control are discussed.

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Epidemiology: past, present and future

Tuberculosis is an ancient human disease that can be traced back to Egyptian mummies. Until the beginning of the 1990s, tuberculosis was considered a disease under control with decreasing political and industrial interest. Since then, both the development of multidrug resistant (MDR) strains and the increasing problem of co-infection with human immunodeficiency virus (HIV), have led to a new exacerbation of disease spread that has restrengthened the urge to develop new strategies and drugs. To date, the estimated tuberculosis incidence has risen to 8.8 million worldwide.⁶ While in Western Europe the tuberculosis burden has decreased in recent years, the disease has spread with the growing global population, especially in Asia and Africa, with a 2.7% mean annual increase between 2004 and 2008.⁷ Eighty percent of all tuberculosis cases occur in India, China, South Africa, Nigeria, and Indonesia.⁶

Recent developments

So far, all attempts to limit the global tuberculosis burden have been counteracted by two major obstacles. First, the continuous increase in cases of MDR tuberculosis, which will be one of the most difficult challenges to overcome in the future. By definition, MDR tuberculosis strains are at least resistant to both rifampicin and isoniazid, two commonly used antituberculosis drugs.⁸ The proportion of MDR tuberculosis cases is growing, especially in Eastern Europe. This presents a serious threat to the low-incidence in Western countries. In 2008, 440,000 cases of MDR tuberculosis were reported to the WHO.⁴ Of these, only a small percentage had been previously treated for tuberculosis – that is, most of the cases result from primary transfer of multidrug-resistant strains. The use of monotherapeutic agents like isoniazid in many cases leads to selection of resistant mutants, which have previously acquired resistance to multiple other tuberculosis drugs.^{9,10} In addition to MDR strains, there has been a recent increase in the number of cases caused by strains that are extensively resistant (ie, resistant to fluoroquinolone and one aminoglycoside) or even resistant to all currently available antituberculosis drugs.¹¹ Already about 5% of all new tuberculosis cases are due to MDR strains, with more than half of all MDR cases occurring in China and India. In the Russian Federation, MDR tuberculosis is found in 25% of all newly diagnosed patients. It is estimated that there are at least 50,000 cases of extensively drug-resistant tuberculosis, with a total of 58 countries reporting such cases to the WHO.¹² This dramatic increase establishes the need for efficient diagnosis of drug resistance in newly diagnosed

tuberculosis cases. However, the lack of reliable phenotypical and genotypical characterization methods in countries with high MDR burden limits a definitive approach and emphasizes the use of aggressive first-line therapy.

Secondly, the exploding number of HIV-associated tuberculosis infections has contributed to the continuous increase of tuberculosis cases over the last few years. Almost one in seven global tuberculosis cases is associated with HIV, and about 80% of these are found in sub-Saharan Africa.¹ However, only 34% of tuberculosis patients are tested for HIV worldwide.⁶ Over the last few decades, the risk factors associated with tuberculosis susceptibility have changed dramatically. While malnutrition and poverty are still strongly associated with the risk of infection with tuberculosis in developing countries, HIV has gained a central role among risk factors, and the threat of developing active tuberculosis is more than 20 times greater in HIV-infected people.¹³

Smoking is also associated not only with the risk of infection (up to 70% increase) but also with disease progression (up to 50% increase).¹⁴ Furthermore, diabetes mellitus has been reported to enhance the risk for developing active tuberculosis by about three times.¹⁵ Although tuberculosis treatment in Europe at the beginning of the twentieth century consisted of phototherapy in areas with high sun exposure, it was not until 1985 that the connection between vitamin D deficiency and tuberculosis was identified.¹⁶ Research on the underlying cellular mechanism finally suggested that cathelicidin, an antimicrobial peptide regulated by vitamin D, is a key player in host defense against tuberculosis.¹⁷ Recently, genetic variants in the vitamin D receptor have also been linked to disease susceptibility.¹⁷

Furthermore, a risk factor that nowadays plays a critical role, especially in Western countries, is immunosuppression due to malignancy or immunosuppressive drugs. Treatment with tumor-necrosis-factor antagonists in patients suffering from rheumatoid diseases has emerged as a central problem leading to reactivation of dormant tuberculosis.¹⁸

Current management approaches and challenges

Current management approaches concentrate on three different areas: (1) detection of infected individuals; (2) control of patient migration and disease spread; and (3) individual treatment, with a focus on drug resistance.

Identification of infected individuals

From an epidemiological point of view, migration is one of the factors that drives the spread of tuberculosis. Not only

does migration from high- to low-burden countries lead to increased disease incidence, it is also the main causative factor in the spread of MDR tuberculosis, for instance, from Eastern to Western Europe. While the most effective way to control tuberculosis is by reducing the tuberculosis cases in the countries of origin, many low-incidence countries have initiated tuberculosis screening for immigrants. These screening programs, however, are far from standardized. While some European countries screen for tuberculosis with chest X-ray, others use the tuberculin skin test, sometimes supplemented by interferon (IFN)- γ assays.¹⁹

A major obstacle to global tuberculosis control is the lack of reliable biomarkers for different stages of tuberculosis infection. According to current WHO guidelines, cultural verification of the bacteria remains the diagnostic gold standard.²⁰ However, culture of the causative agent of tuberculosis can take up to 6 weeks and requires specific laboratory equipment. This makes initial therapeutic approaches difficult, since infected individuals who have not unequivocally been diagnosed continue to spread the disease. Therefore, sputum smear analysis is recommended. According to new WHO guidelines, only one positive smear result (instead of two) suffices to define a tuberculosis case. One has to keep in mind, however, that the diagnostic conclusiveness of microscopy approaches is quite dependent on the experience of the microscopist, with sensitivity ranging between 32% and 97%.^{21,22} For several decades, the standard screening test for infection with *M. tuberculosis* was the tuberculin skin test. In the case of a positive test result, the delayed hypersensitivity response can be observed up to 72 hours after intradermal injection of tuberculin. Downsides of this test are the lack of specificity for *M. tuberculosis* and the high rate of false-positive results in people who have received Bacille Calmette-Guérin (BCG) vaccination as well as in children or immunosuppressed patients.²³ IFN- γ -release assays are used to eliminate these caveats. Over the last 10–15 years, new immunological tests have been developed that are now widely used in clinical practice. Both use IFN- γ secretion from T cells as a specific marker of tuberculosis infection. In contrast to the tuberculin skin test, they use specific protein antigens from *M. tuberculosis*, thus avoiding false-positive results after BCG vaccination. In these tests, either single IFN- γ -secreting T cells are counted using an enzyme-linked immunospot technique-based approach, or IFN- γ secretion is measured in a blood sample via enzyme-linked immunosorbent assay after antigen stimulation. These approaches have a high sensitivity (up to 90%) for individuals with latent tuberculosis infection as well as patients with active disease.^{24,25}

The tests described require much less time but are also not as stringent as the gold standard for tuberculosis diagnosis, which is the culture of *M. tuberculosis* from patient samples. As previously mentioned, culture of the causative agent of tuberculosis is a lengthy procedure, so IFN- γ tests provide a substantial improvement in early diagnosis for both latent infection and active disease. Thus, these methods might help identify early sources of infection and help limit disease spread, provided that they become broadly and cost-effectively available in high-burden countries.²³

Current treatment options

Once identified, patients suffering from tuberculosis must undergo immediate treatment. The current WHO guidelines are based on the internationally agreed strategy for tuberculosis control (the Directly Observed Treatment Short course [DOTS]).²⁶ The recommendations in this program include not only standardized treatment and patient care but also effective disease management and drug supply.²⁶ The regime currently recommended consists of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months. Subsequently, patients with newly detected pulmonary tuberculosis receive isoniazid and rifampicin for another 2 months. For an optimal outcome, the treatment should be given daily.²⁰

If a person has previously undergone tuberculosis treatment, drug susceptibility testing is advised, at least for isoniazid and rifampicin. As the treatment of drug-resistant tuberculosis has recently been summarized,²⁷ treatment options in the case of MDR tuberculosis are only briefly outlined here and, instead, focus is on the recently emerging challenge of treating tuberculosis patients with HIV co-infection. General WHO recommendations for MDR tuberculosis include 2 months of isoniazid, rifampicin, pyridazinamide, ethambutol, and streptomycin, followed by 1 month without streptomycin and continuous use of isoniazid, rifampicin, and ethambutol for 5 more months.²⁰ Nonetheless, the new WHO guidelines strongly recommend drug susceptibility testing whenever possible due to rising multidrug resistance and the likelihood of nonoptimal drugs in the regimen. During the therapy, monthly smears and cultures should be analyzed to monitor conversion. The treatment should be continued in the case of MDR tuberculosis for at least 18 months after culture conversion to ensure stable therapy success, which is achieved in about 65% of patients. Although not yet sufficiently corroborated by empirical data, experts suggest ethambutol, pyrazinamide, a fluoroquinolone, and an intravenous drug like capreomycin for MDR-tuberculosis treatment.^{28,29} The optimal duration of

treatment needs to be evaluated in further studies. Although several other drugs have been shown to be effective in the treatment of MDR tuberculosis, severe side effects limit their use as safe long-term treatment, as is exemplarily demonstrated by linezolid.³⁰ Apart from the requested sputum culture conversion, severe side effects like peripheral or optic neuropathy occurred in a substantial number of patients in a relatively short period of treatment time. For extensively drug-resistant tuberculosis, the available data is even more limited, emphasizing the need for new drugs.

Treatment of HIV/tuberculosis co-infection

A special situation applies to tuberculosis patients who are co-infected with HIV. This combination is the major reason for the rising prevalence of tuberculosis in sub-Saharan Africa. The risk for tuberculosis infection is increased from the start of HIV infection and is especially enhanced with a CD4⁺ T cell count of <500/ μ L.^{31,32} In individuals co-infected with HIV and tuberculosis, treatment with highly active antiretroviral therapy (HAART) plus the above-mentioned state-of-the-art tuberculosis treatment is desirable. Currently, however, several drug–drug interactions might lead to further complications in patients who are simultaneously treated for both diseases. Specifically, the use of protease inhibitors is often limited when given in combination with rifampicin. In this case, rifabutin is preferred.³³ Several different measures are taken to reduce the number of HIV/tuberculosis co-infected patients. First, the routine HIV testing is increasingly implemented to identify those with HIV, especially in areas with high tuberculosis incidence. Second, the WHO now recommends prophylaxis with cotrimoxazole, which has proven beneficial in patients with and without tuberculosis with respect to mortality and CD4⁺ T cell counts.³⁴ In addition, early and rigorous treatment of HIV in newly diagnosed individuals is strongly indicated, as the risk of tuberculosis infection is decreased under HAART, and mortality is reduced by up to 95% in infected patients.^{35,36} This is further underlined by the finding that mortality increases by up to 56% if antiretroviral therapy is delayed until after successful treatment of tuberculosis.³⁷

An unsolved problem is the large number of cases with confirmed HIV and suspected tuberculosis. Here again, more intensive screening would lead to beneficial individual treatment and reduced transfer. Another limiting factor for combined tuberculosis/HIV treatment can be the development of an immune reconstitution inflammatory syndrome,

which is seen in patients with preexisting tuberculosis that show clinical worsening after initiation of HAART.³⁸ The combined therapy, therefore, should be monitored by experts in both fields. When combined with multidrug-resistant or extensively drug-resistant tuberculosis, the outcome is dramatically worsened and the need for a new therapy even greater.⁹

With respect to morbidity and mortality in co-infected individuals, prevention of co-infection is an important aim. Isoniazid is recommended for prevention and latent tuberculosis infection, as it reduces the risk of tuberculosis in HIV-infected people by one-third.³⁹

Emerging strategies to combat tuberculosis: current chances and challenges

As outlined, the epidemic of multidrug-resistant tuberculosis threatens to undermine the success that has been achieved with available treatment.⁴⁰ Currently existing technologies can only partly counter this problem. In addition, three novel avenues have to be pursued to combat the increasing problem of multidrug resistance. First, new diagnostic tests are urgently needed for drug-resistant and drug-susceptible tuberculosis. Laboratory expertise must be expanded in a cost-effective manner and reliable biomarkers for the diagnosis of the state of the infection need to be made available.⁴¹ Second, new antituberculosis drugs are being developed, many of which might prove effective against existing drug-resistant tuberculosis strains.⁴² Third, the introduction of a new effective vaccine could be a breakthrough in tuberculosis control.⁴³ Effective prevention is the ultimate goal on which all currently emerging strategies to combat tuberculosis need to converge.

Some of the recent approaches to the design of new anti-tuberculosis drugs and vaccines will now be summarized, the basic mechanisms underlying their function will be explained, and a brief overview of the status or the development and testing of these substances will be given.

Drug development

Currently available drugs for tuberculosis are insufficient to challenge the emerging problems of treatment, and the development of new drugs has become a major priority in the global effort to reduce worldwide tuberculosis burden. Over the last decade, several new drugs have entered the clinical pipeline, the most promising of which are summarized in Table 1.

Table 1 Potential candidates for new antituberculosis drugs

Drug candidate	Mechanism	Attributes
TMC-207	Targeting of ATP synthase	Efficacy proven in animal model and clinical trial; novel pharmaceutical target
PNU-100480	Linezolid-analog, targeting ribosome	Novel pharmaceutical target
SQ-109	Ethambutol-analogue, targeting cell-wall synthesis	Efficacy proven in animal model
OPC-67683 and PA-824	Prodrug; bioreactive activation	Potentially effective against latent tuberculosis

Abbreviation: ATP, adenosine triphosphate.

Generally, new antituberculosis drug candidates need to have certain characteristics to be successful.⁴⁴ First, it is highly desirable to shorten the treatment of infected patients, and to treat latently infected individuals. Thus, new drugs need to show efficacy against both dormant and replicating *M. tuberculosis*. Furthermore, as substances active against MDR tuberculosis are urgently needed, the molecular mechanisms of action must be novel, hence, new drug candidates must have target structures that are not directly attacked by currently available antibiotics. Second, new drug candidates must be safe. This is especially important since children and pregnant women are population groups which are highly affected by tuberculosis in some countries.⁴⁵ Therefore, new drugs will only prove efficient if their tolerability profile includes these two important population groups. Third, a necessary attribute of any new drug against tuberculosis is its affordability, thus, low cost of production, storage, and distribution are high on the drug research agenda. Fourth, since new antituberculosis drugs will need to be co-administered with antiretroviral drugs, drug–drug interactions of such combinations need to be extensively tested. Likewise, it is desirable that new drugs be able to be administered orally and suitable for application once a day.

Among the new compounds potentially meeting these criteria is TMC-207, which acts by inhibiting adenosine triphosphate (ATP synthase).⁴⁶ A high-throughput screen using *Mycobacterium smegmatis* led to the discovery of TMC-207 and, together with rifapentine and pyrazinamide, it was effective in a mouse model of tuberculosis. First clinical assessment in placebo-controlled double-blind randomized trials showed promising results, verifying ATP synthase as a potential drug target.⁴⁴ When added to standard therapy for MDR tuberculosis, TMC-207 reduced the time to conversion to a negative sputum culture.⁴⁷

In addition, PNU-100480, an analog of the oxazolidinone linezolid, and SQ-109, a derivative of the ethylenediamine ethambutol, showed efficacy in a mouse model of tuberculosis when substituted for standard regimen components.^{48,49} Both compounds have entered clinical trials and their assessment is in progress.⁵⁰

Finally, two members of the nitroimidazole family, OPC-67683 and PA-824, are being assessed in clinical trials.⁵¹ Like all nitroimidazoles, their bactericidal function is believed to stem from reactive species generated through bioreductive activity.⁵² Early results suggest that the maximum potency of these substances can be achieved with doses of as little as 200 mg per day.⁴⁴

This overview of some new drug candidates is by no means comprehensive, but gives an insight into current hopes and obstacles in the development of new antituberculosis treatments. With the drug candidates described, the end of the pipeline is still far from being reached. Instead, ongoing basic research is needed to identify drug combinations that prevent the rapid development of multidrug resistance, to develop easier forms of application, and to gain knowledge about potential drug–drug interactions. Ideally, a combination of drugs would act in a potent, synergistic manner, target multiple structures to circumvent the generation of drug-resistant strains, and avoid complications with co-administered antiretroviral drugs. To achieve this goal, not only is progress in basic research needed but also clear guidelines for the development of new regimens. Owners of the individual drugs will also need to cooperate and allow combinations of compounds to be tested and refined.

Vaccine development

While advances in the treatment of tuberculosis are undoubtedly necessary to reduce global disease burden, the ultimate goal must be to achieve effective prevention through sterile eradication, that is, the complete elimination of *M. tuberculosis* from the host after infection. The only means to achieve this aim is through the development of an effective vaccine.⁵³ The current vaccine for tuberculosis, BCG, has quite an impressive record with respect to its safety and low cost. BCG has been used in more than 4 billion individuals over the last decades and protects against severe childhood tuberculosis. However, for various reasons, the vaccine fails to satisfactorily prevent adult pulmonary disease, and is therefore not sufficient to combat the epidemic.⁵⁴

Table 2 Pipeline of vaccine candidates that are currently in clinical trials

Category	Vaccine candidate	Mechanism	Clinical trial
Live vaccines as BCG replacement	AERAS-422	Expression of perfringolysin O to allow escape into the cytoplasm Expression of immunodominant antigens 85A, 85B and Rv3407	Phase I
	rBCG Δ ureC:Hly	Listeriolysin enables BCG to escape from the endosome to enhance antigen cross-presentation UreaseC-deficiency ensures optimal pH for listeriolysin activity	Phase I completed
Subunit vaccines as BCG boost: viral vectors	Ad5Ag85A	Adenovirus type 5 expressing mycobacterial antigen 85A	Phase I
	AERAS-402	Adenovirus type 35 expressing 85A, 85B and TB10.4 as a fusion protein	Phase II
Subunit vaccines as BCG boost: protein/adjuvant formulations	MVA85A	Modified vaccinia virus Ankara expressing antigen 85A	Phase IIb
	HyVac4	Fusion protein of TB10.4 with antigen 85B plus adjuvant MPL or IC31	Phase I
	Hybrid I	Fusion protein of ESAT-6 with antigen 85B plus adjuvant CAF01 or IC31	Phase I
	M72	Fusion protein of Mtb32 and Mt39 plus adjuvant AS02A	Phase IIa completed
Therapeutic vaccines	Mycobacterium vaccae RUTI [®]	Whole-cell vaccine (inactivated)	Phase I
		Detoxified liposomal cellular fragments of <i>M. tuberculosis</i>	Phase I completed

Abbreviation: BCG, Bacille Calmette-Guérin.

In principle, one has to distinguish two general approaches toward vaccination strategies against tuberculosis. Pre-exposure vaccination aims at preventing disease in individuals who have not yet encountered the pathogen *M. tuberculosis*. In contrast, postexposure vaccination tries to inhibit disease outbreak in people who are already infected. Although an estimated 2 billion humans harbor the pathogen, 90% of whom are not developing active disease, the former category is the one that most novel vaccine candidates belong to. So far, effective vaccine development has been hampered by the lack of reliable biomarkers to efficiently distinguish between noninfected individuals, latently infected subjects, and patients with active disease.⁵⁵ Furthermore, despite recent progress in basic research, an optimal animal model to study the efficacy of novel vaccine candidates in vivo is still lacking.

There are several categories of new vaccine candidates.⁵⁶ The first builds on the safety and efficacy of BCG. Recombinant BCG strains have been optimized with respect to their immunogenicity and the expression of immunodominant *M. tuberculosis* antigens.⁵⁷ The second group can be used for boosting strategies, subsequent to BCG or a recombinant BCG. The rationale behind this group is to deliver antigens with an immunodominant effect, or antigens associated with dormancy, in an immunostimulatory context. This immunostimulation can be achieved either through viral vectors or through the combination with adjuvants.⁵⁸ Finally, two candidates can be described as “therapeutic vaccines”

and comprise whole attenuated mycobacteria. The vaccine candidates that are currently in clinical trials are described in detail in Table 2.

What does a possible scenario for the application of these new vaccine candidates look like? Optimally, future vaccinations may consist of several coordinated steps. During early infancy, a highly efficient BCG replacement will be given as a primer. In later infancy, booster vaccines, which, in the best case, include several antigens from different stages of the mycobacterial life cycle, will be administered. These boosters will conceivably be given either as protein/adjuvant formulations or in the form of viral vectors – whichever proves more efficient and safe. In infants, booster vaccines should optimally consist of a large antigenic spectrum of metabolically active *M. tuberculosis*. However, it might be effective to include dormancy antigens in vaccine formulations administered to adults. Together, these heterologous prime-boost strategies will potentially prove far superior in comparison with the current BCG vaccine.⁵⁹

Conclusion

Tuberculosis is still a major cause of death worldwide and a central problem for global health. The disease, although both preventable and treatable in principle, has been neglected for decades and, thus, both research and disease management progress has stagnated for far too long. In the last decade, however, the first steps have been made to improve the

prevention, detection, and treatment of tuberculosis, not only in the economically developed world, but also with an increasing focus on poor countries.⁸ To initiate this development, a paradigm shift was necessary. First, there is an increasing awareness that tuberculosis is not a conquered disease; rather, the disease is a larger global health problem today than ever before. Second, tuberculosis is a major roadblock to economic development in poor countries, and lack of economic development impedes the epidemiological control of tuberculosis. This vicious circle at the intersection of tuberculosis and poverty needs to be broken to provide sustained progress in the management of the disease. Third, tuberculosis is no longer considered solely a public health problem. Instead, the problem needs to be tackled as a wider development issue, including in terms of education, hygiene, public policy, housing, and social development.

The way to achieve this goal is through fostering public-private partnerships. Incentives must be created for infectious disease researchers, pharmaceutical companies, and global health institutions to work together with the aim of initiating the next steps toward reaching the United Nations Millennium Development Goal number 6,²⁶ which includes reducing the global burden of tuberculosis.

As summarized in this review, many challenges remain. Defining clear biomarkers for tuberculosis diagnosis, removing financial barriers to treatment, and testing safety and efficacy of novel vaccine and drug candidates will be some of the most pressing goals to achieve in the near future.⁶⁰ Nonetheless, the developments of the last decade, as exemplified in this review, and new partnerships to fight this ancient disease have opened new avenues to reach the goal of reducing global tuberculosis burden in the coming years. There is hardly any other field of biomedical research and disease management that can foster global socioeconomic development as much as the current fight against tuberculosis.

Disclosure

The authors report no conflicts of interest in this work.

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