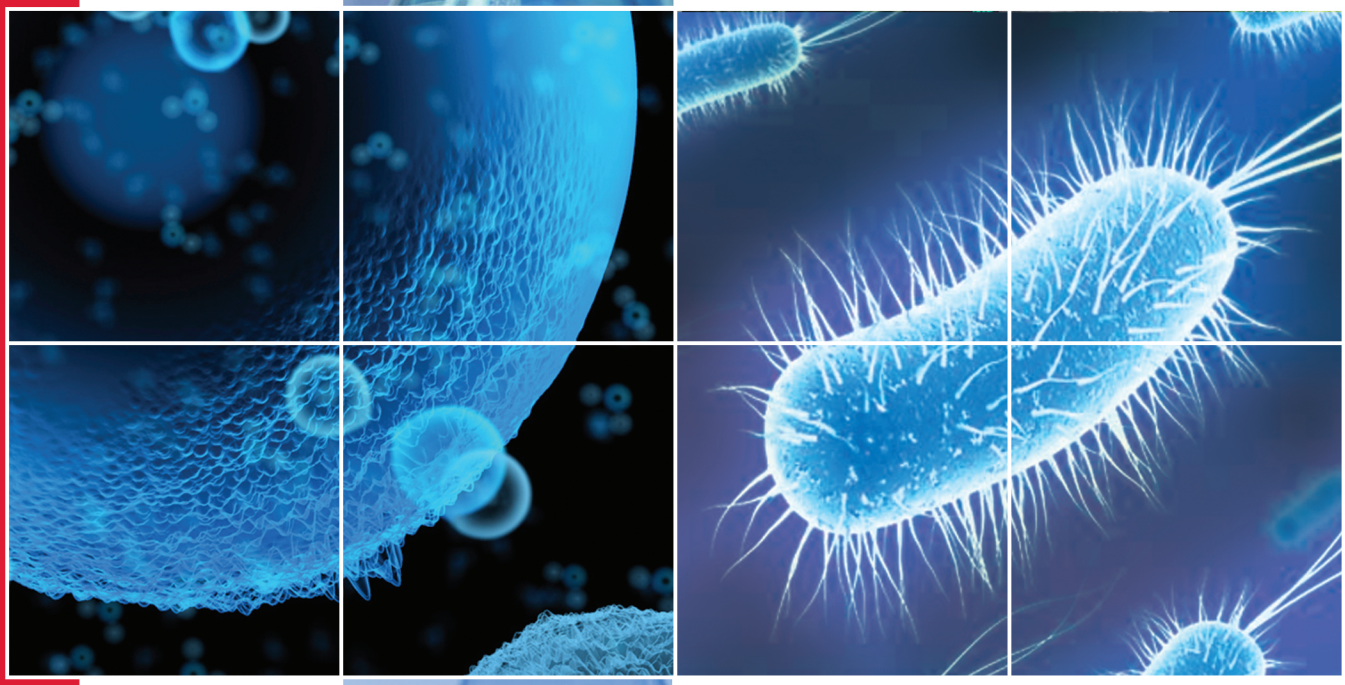
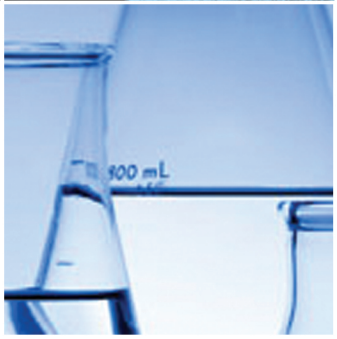
Frontiers in Anti-Infective Drug Discovery

Editor:
M. Iqbal Choudhary





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Frontiers in Anti-Infective Drug Discovery

(Volume 10)

Edited By

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PREFACE

The global COVID-19 pandemic has highlighted the importance of the prevention and treatment of infectious diseases. Today the world is faced with an increasing number of emerging and re-emerging infectious diseases and the imminent threat of the next global-scale pandemics. Neglected tropical diseases continue to affect a large number of people globally. Multi-drug resistance infections have made the treatment of even common infections a major challenge. In this context, continuous efforts to discover and develop safe and effective anti-infectious agents are imperative. Recent advances in genomics, molecular and structural biology, and enabling technologies, such as high throughput screening, have greatly improved our capacity to identify new molecular entities against prevalent, neglected, and rare infectious diseases. In this process, the identification of new drug targets plays a central role.

The 10th volume of *Frontiers in Anti-Infective Drug Discovery* reflects our continuous efforts to highlight the most recent and exciting developments in this crucially important field. The current volume is a collection of four comprehensive reviews, each focused on a specific aspect of anti-infective drug discovery and development.

Venkatesh *et al.* in their review focussed on the management and treatment of a common eye infection, called posterior segment ocular infection, caused by a range of microorganisms (bacterial, fungal, and viral). Authors have highlighted the challenges faced in the treatment of ocular infections, and recent advances in chemotherapeutic agents for the successful management of this debilitating disease.

Malaria, particularly drug-resistant malaria, is re-emerging as a major cause of global concern, resulting in increasing morbidity and mortality. Moyo *et al.* have contributed an article that highlights the major challenges in the development of anti-malarial drugs, and then focuses on a novel strategy for reversing the drug resistance in *Plasmodium falciparum* against old antimalarial agents, including artemisinin-based agents. Authors have discussed many of such drug resistance reversal agents, their current status of development, and the way forward.

Enabling technologies, particularly “omics” now play a key role in the field of anti-infectious drug discovery. Guerrero *et al.* have provided a comprehensive account of the unprecedented role of “omics” technologies, particularly genomics, metagenomics, transcriptomics, proteomics and metabolomics, in the rapid and cost-effective identification of anti-infectious drug leads, and their further development through pharmacological assessment and clinical trials.

Last but certainly not least, Akarsu and Polat have contributed a chapter on a very interesting aspect of the adverse effects on the skin as a result of vaccination. The authors have highlighted the reported cases of cutaneous adverse effects of various anti-infective vaccines based on an extensive literature review.

The 10th volume of the *e*book series is the result of efficient coordination and excellent management of the entire team of Bentham Science Publishers, and most importantly timely submissions from the authors. We greatly appreciate the efforts of Miss Asma Ahmed (Manager Publications) and the team leader Mr. Mahmood Alam (Director Publications) for putting together an excellent compilation of well-written articles. We sincerely hope readers will benefit from this excellent compilation of the most recent scientific work in the important field of anti-infectious drug discovery.

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CHAPTER 1

Managing Posterior Segment Ocular Infections: A Review of Pharmacotherapy

Saurabh Verma[1], Abhidnya Surve[1], Shorya Vardhan Azad[1], Kumar Parmanand[1], Vinod Kumar[1], Rohan Chawla[1] and **Pradeep Venkatesh[1,*]**

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Abstract: Ocular infections affecting the posterior segment of the eye can lead to severe visual disability. The infections can range from bacterial/fungal endophthalmitis to various types of viral retinitis to toxoplasma retinitis. In recent years there have been significant advances in the use of chemotherapeutic agents for managing these infections. In this review we discuss their management with anti-infective agents. The choice of drugs, alternatives, mode of delivery and duration of therapy are discussed.

Keywords: Acute retinal necrosis, Antibiotics, Antifungals, Antiviral, Chickengunya, CMV retinitis, Dengue, Endophthalmitis, Intravitreal, Measles, Ocular drug delivery, Toxoplasma chorioretinitis, Viral retinitis.

INTRODUCTION

Endophthalmitis

Endophthalmitis is the inflammation of inner ocular coats with exudation into the vitreous cavity, secondary to infection by a microorganism. Toxins produced by infectious agents along with host's immune response can cause rapid and irreversible damage to retinal tissue with the potential to cause blindness. Thus, endophthalmitis is a grave ophthalmic emergency.

Based on the mode of infection, endophthalmitis may be classified as exogenous or endogenous [1]. In exogenous endophthalmitis, there is an identifiable mechanism of intraocular seeding of an organism from an external route. Exogenous endophthalmitis is the most common type (>90%) and can further be classified as follows:

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1- On the basis of mode of entry of infectious agent- post surgical, post intravitreal injection, post-traumatic, bleb-related endophthalmitis or associated with corneal ulcer.
2- On the basis of onset of symptoms and duration- acute onset, late onset, chronic.
3- On the basis of causative organism- bacterial, fungal, protozoal.

Endogenous endophthalmitis is an intraocular infection resulting from hematogenous spread from a primary focus of infection elsewhere in body and accounts for 2-8% of all cases of endophthalmitis [2, 3].

Acute post-operative endophthalmitis is the most common type of endophthalmitis, with cataract surgery, intravitreal injections and secondary intraocular lens implantation being the most common causes [4]. Normal flora of the eyelids and conjunctiva are frequent sources of contamination. Other potential sources, include contaminated instruments/ solutions, contaminated water, microbes in the air and resident on the surgeon and other personnel in the operation theater. Common causative organisms of endophthalmitis are summarized in Table **1** [1, 5 - 11].

Table 1. Common organisms causing endophthalmitis.

1.	Acute onset post-operative endophthalmitis- *Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus viridans*
2.	Delayed onset post-operative endophthalmitis- Propionibacterium species, Candida species, *Staphylococcus epidermidis*
3.	Post traumatic endophthalmitis- *Staphylococcus aureus, Bacillus cereus*
4.	Post intravitreal injection endophthalmitis- *Staphylococcus epidermidis, Streptococcus viridans*
5.	Bleb associated endophthalmitis- *Streptococcus viridans*, *Haemophilus Influenzae*, *Staphylococcus species*
6.	With microbial keratitis- Gram negative organisms, *Staphylococcus aureus*
7.	Endogenous endophthalmitis- *Candida* species, *Aspergillus* species

Sample Collection and Lab Testing

Identification of causative organisms and their susceptibility to anti-microbial drugs is important in managing patients with endophthalmitis, particularly when there is poor response to injections given earlier on, based on empirical recommendations. Conjunctival swab and corneal biopsy can be sent for culture in presence of coexisting purulent discharge or corneal ulcer, respectively. Anterior chamber tap with a 27-gauge needle can also be useful but is of limited use because of poor rate of isolation [12].

Since vitreous is the primary site of organismal colonization in endophthalmitis, vitreous samples tend to yield the highest rate of positive culture or staining. Vitreous tap can be taken through a 23-gauge needle inserted through the pars plana route [13]. However, attempt to suck vitreous without cutting it first often results in a dry tap or inadequate sample. Also, inadvertent pull on the vitreous can also result in the formation of iatrogenic breaks and retinal detachment. Vitreous biopsy with a pars plana vitrectomy probe avoids the aforementioned complications and is considered a safer option. Usually, 0.2 ml to 0.3 ml of undiluted sample is considered adequate for various tests [14]. It is advisable that vitreous biopsy should be done without switching on infusion as it may result in dilution of the collected sample [15].

Gram and KOH staining can help in making an immediate distinction between fungal or bacterial endophthalmitis. For KOH preparation, a fresh sample is necessary. Both bacterial and fungal cultures should be sent at the earliest to recognized and experienced laboratories. In addition to culture, drug sensitivity tests should also be obtained. It is advisable to wait for 1 week and 2 weeks respectively for bacterial and fungal culture before declaring no growth [16]. Commonly used bacterial and fungal cultures are summarized in Table **2** [15 - 17].

Table 2. Commonly used bacterial and fungal culture media.

-	Media	Type of Organism Isolated
Bacterial cultures	Chocolate agar	Fastidious pathogens such as Neisseria and Haemophilus
-	Blood agar	Almost all bacteria
-	MacConkey agar	Gram negative enteric bacilli
-	Eosin methylene blue agar	Gram negative enteric bacilli
Fungal cultures	Sabouraud's Dextrose agar	All fungal organisms; especially useful for dermatophytes
-	Brain heart infusion agar	All fungal organisms

Bacterial Endophthalmitis

Intravitreal injection of the antibiotics is the preferred modality for drug delivery, as it achieves the required antibiotic concentration in the eye. Additional modes of antibiotic administration can be topical, intravenous and/or oral. A combination of the above modes is used according to clinical presentation and severity of symptoms.

CHAPTER 2

Discovery and Development of Antimalarial Drug-Resistance Reversal Agents

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Abstract: Despite the meritorious measures taken to curb the malaria scourge in the last two decades, the drug-resistance phenomenon threatens to reverse the gains made. Evidence of partial resistance against the first-line antimalarial drugs, the artemisinin-based combination therapies, in Africa, a region that accounts for 95% of global malaria cases, has aroused fears that it could spread fast and significantly jeopardise malaria control and eradication efforts. While the antimalarial drug discovery pipeline has several, encouraging candidates emerging through it, unfortunately, the attrition rate is high, with some candidates failing either in preclinical studies or clinical trials. Moreover, the rate of emergence of drug-resistant *Plasmodium* parasite strains far exceeds that of the drug discovery and development process. These challenges demand novel strategies to complement the discovery and development of new therapeutics. One such strategy is the reversal of *Plasmodium falciparum* resistance to old antimalarials by combining these drugs with agents that specifically target drug-resistance mechanisms. This strategy has been successfully used in the antibiotics field, with a classical successful example being the amoxicillin and clavulanic acid combina-

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tion. In this chapter, we present a case for the need to discover and develop antimalarial drug-resistance reversal agents to prolong the efficacy and use of currently available antimalarial quinoline drugs as well as the re-use of old antimalarial quinoline drugs that have been rendered ineffective by drug-resistance. Furthermore, we provide an overview of noteworthy significant innovations that have been made in the field in search for antimalaria drug-resistance reversal agents. We conclude by providing perspectives on how these efforts can be expedited.

Keywords: 4-aminoquinoline, Chloroquine, Drug-resistance, Malaria, *Plasmodium falciparum*, *P. falciparum* chloroquine resistance transporter (*Pf*CRT), Mefloquine, *P. falciparum* multidrug-resistance-1 (*Pf*MDR1) transporter, Quinine, Quinolines, Resistance breakers, Resistance reversal agents.

INTRODUCTION

Malaria: A Health, Economic and Social Challenge

Malaria, a tropical disease caused by an infection with unicellular parasitic protozoa of the genus *Plasmodium* transmitted by female *Anopheles* mosquitoes, has been a major health challenge to human beings since time immemorial, with documentation from as far back as 2700 BC making reference to the disease [1]. It is presently endemic in 85 countries with half the world's population at risk of getting infected [2]. Despite the concerted intervention measures, malaria remains a serious global public health burden. In 2020, it caused 241 million clinical cases resulting in 627 000 fatalities, with the World Health Organisation (WHO) Africa Region accounting for nearly 95% of those cases (Table **1**) [2]. Children under the age of 5 years are amongst the most vulnerable, along with pregnant women, accounting for 77% of the deaths (Table **1**) [2].

The impact of malaria extends beyond the compromise of the wellbeing of its victims to having a negative impact on the economy [3, 4]. There is concurrent poverty and economic burden on both individuals and the healthcare systems in malaria-endemic countries. For example, it has been reported that Africa is losing close to US$12 billion of its Gross Domestic Product (GDP) per year while also causing stagnation in economic growth by as much as 1.3% [4]. Since 2001, countries in sub-Saharan Africa have been spending on average US$300 million annually on malaria case management, a staggering amount to countries whose meager income resources are already overburdened and stretched by other pressing issues [3, 4]. In addition to the loss of household incomes, malaria also leads to work and school health-related absenteeism [3, 4], with the latter having been reported to range between 17 and 54% in some parts of Kenya [5].

Table 1. The health burden of malaria*.

WHO Region	Malaria Cases	Malaria Deaths	Health burden: Children and Pregnant Woman
Africa	228 000 000	602 000	▪ 77% deaths were children <5 years ▪ In 33 African countries, 11 600 000 pregnancies were exposed to malaria resulting in 819 000 children with low birth weight
South-East Asia	5 000 000	9 000	
Eastern Mediterranean	5 700 000	12 300	
Western Pacific	1 700 000	3 200	
Americas	650 000	409	

*Source [2].

Malaria Control: The Perpetual Challenge of Drug-Resistance Emergence and Spread

Along with vector control, chemotherapeutic agents including the quinolines (Fig. **1**) and artemisinin-based combination therapies (ACTs), have been decisive in the control of malaria [6]. Unfortunately, the use of antimalarial drugs has, historically and presently, been undermined by the emergence and spread of drug-resistant *Plasmodium* parasite strains (Table **2**) [7, 8]. This has rendered drugs, such as Chloroquine, less effective, significantly curtailing their role and deployment in malaria control efforts.

Table 2. Antimalarial drug development and resistance emergence*.

Drug	Discovered	Launched	Resistance First Report	Resistance Associated Gene Mutations
Quinine	1820	19th century	1910	*pfmdr1, pfmrp, pfnhe1*
Chloroquine	1936	1945	1957	*pfcrt, pfmdr1, pfmrp*
Proguanil	1945	1948	1949	*pfdhfr*
Amodiaquine	1940s	1940s	1954	*pfcrt*
S-P$^{\infty}$	-	1967	1967	*pfdhps*
Artemisinin	1970s	1970s	2009	*kelch13*
Mefloquine	1970s	1970s	1982	*pfmdr1*
Halofantrine	1970s	1988	1992	*pfmdr1*
Atovaquone	1980s	1996	1996	*pfcytb*

*Source [9 - 14]. $^{\infty}$S-P – sulphadoxine-pyrimethamine; *pfmdr1 – P. falciparum* multidrug resistance 1; *pfmrp – P. falciparum* multidrug-resistance-associated protein; *pfnhe – P. falciparum* Na^+/H^+ exchanger; *pfcrt – P. falciparum* chloroquine-resistance transporter; *pfdhfr – P. falciparum* dihydrofolate reductase; *pfdhps – P. falciparum* dihydropteroate synthase; *pfcytb – P. falciparum* cytochrome b.

CHAPTER 3

Omics Technologies and Anti-Infective Drug Discovery

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Abstract: The design of novel, safe, and effective drugs of natural origin is a challenging issue. To screen and uncover the infinite world of antimicrobial agents derived from secondary metabolites for drug discovery requires the integration of high-throughput technologies such as biology systems (bioinformatics) and omics technologies. These technologies include genomics, metagenomics, transcriptomes, proteomics, and metabolomics). In the present chapter, we focused on revisiting several aspects of these technologies in order to emphasize their unprecedented contribution to drug discovery. In addition, they represent a step forward in pharmacological and clinical research.

Keywords: Anti-infective agents, Omic technologies, Drugs system biology, Secondary metabolites, Bioinformatics.

INTRODUCTION

The anti-infective agent compounds used against pathogenic and resistant bacteria can be either natural or synthetic. Herein, we focused on the naturally derived compound designed as a drug, targetable to any physiological process of the microbial organism. Marine ecosystems represent an enormous richness, a vast repertoire of natural products, to be characterized by eliminate their, chemical

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structure or by the mechanism of action; at this point, for example, the marine peptides from which several antimicrobial-like drugs are obtained (Fig. **1**) [1 - 3].

Drug discovery is necessary to optimize the sourcing of scaled strain cultivation, scale production, and the poor growth of the producers that leads to low yield (low amount of the desired compound). However, advances in high- throughput technologies have allowed us to trace a path to approach microbial-community genomes for elucidating biosynthetic gene clusters and natural drug-encoded products.

Next-generation therapeutics shaped by high-performance sequencing methodologies (NGS) allow the exploration and discovery of novel and improved anti-infective drugs. Genomic studies produce large databases of molecular information on potential druggable and targetable proteins, similarly accumulating data on proteomics, metagenomics, and transcriptomics. Next-generation therapeutics shaped by high-performance sequencing methodologies permit the exploration and discovery of novel and improved anti-infective drugs. Genomic studies produce large databases of molecular information on potential druggable and targetable proteins and, in a similar fashion accumulate data on proteomics, metagenomics, and transcriptomics. Furthermore, NGS provides insight into the pattern of gene expression and the pattern of drug discovery. It is essential to harness the power of omics technologies of NGS, and robotic high-throughput screening of the diverse and vast pool of natural compounds and secondary metabolites, in combination with *in-silico* and fragment-based screening techniques, new structural biology methods for rational drug desing, especially high-throughput tools in Metabolomics such as the Matrix-Assisted Laser Desorption/Ionization-Time-Of-Flight (MALDI-TOFF); Nuclear Magnetic Resonance (RMN), Liquid Gas Chromatography (LGC), and other advanced chemical technologies, including combinatorial and parallel synthesis. The pharmacokinetic and metabolic properties of the anti-infective drugs elucidate the development of validated pharmacodynamics end-points and molecular markers of drug response, ideally using non-invasive imaging technologies. Gene-expression microarray technologies are very useful for defining detailed molecular signatures of drug action. This technology can identify on-target and off-target effects and can determine and analyze molecular biomarkers for proof-of-concept studies, pharmacological end points and, to date, the development of new therapeutic agents. Furthermore, structured genomic information employed to identify classes of compounds for which detailed experimental structure-activity studies have been conducted, *e.g*., the identification of Quinones whose pattern of activity correlated strongly with the expression patterns of particular genes. Moreover, microarray technologies have been useful. Other examples in drug discovery involve inhibitors of transcription factors (under conditions of

inflammation and hypoxia, the expression of mPEGS1, regulated by transcription factors) [4], and/or other chronic diseases, including Alzheimer's and Huntington's disease [5 - 8]. Proteomic and metabolomics technologies have made it possible to understand how epigenetics (culture conditions, interspecies cross-talk, stressors, environmental, nutritional factors, genotypes, cell type, and tissues) can modulate metabolic and signaling proteins in the different biologic processes. This approach also depends on the identification of protein-like targets (metabolic enzymes, cell-surface receptors), which can be involved as causal agents in diseases. The knowledge of microbial genomics, transcriptional factors, dynamics in proteomes (different isoforms and post-translational modifications) and, in general, dynamics in biological systems, can lead to biomarker identification and therapeutic targets, while advances in sampling techniques and structure-determination strategies, as well as target-identification methods, represent key steps in marine and earth drug discovery (Fig. **1**) [4, 9].

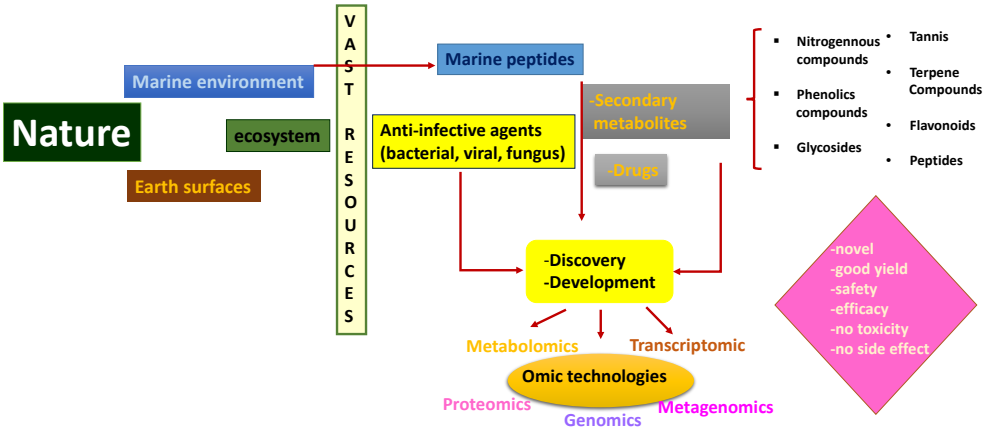

Fig. (1). In nature, hidden and unexplored marine and earth surfaces are a vast resource of natural products with antimicrobial properties. Omics technologies as powerful high throughput tools to approach drug discovery and development.

MECHANISM OF ACTION OF THE ANTI-INFECTIVE DRUGS

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CHAPTER 4

Possible Cutaneous Adverse Effects of Anti-Infective Vaccinations

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Abstract: Although commonly used anti-infective vaccines in clinical practice are generally safe, certain local or systemic adverse reactions related to them may rarely occur. Actually, considering the general vaccination rates, the incidence of serious skin reactions (*e.g* . angioedema, anaphylaxis, Stevens–Johnson syndrome) is very low but vaccine-associated local cutaneous reactions such as erythema, edema, tenderness and pain at the injection sites are one of the most common complications of vaccines. Furthermore, a wide variety of specific or non-specific localized or generalized cutaneous adverse effects (*e.g*. lichenoid eruption, granuloma annulare, pseudolymphoma, erythema nodosum, erythema multiforme, Gianotti-Crosti syndrome, urticaria, lupus erythematosus, bullous pemphigoid, purpura) have been reported in the literature related with commonly used anti-infective vaccines. In this chapter, these adverse cutaneous reactions potentially associated with anti-infective vaccines were summarized with a comprehensive literature review.

Keywords: Adverse reaction, Anti-infective vaccination, Bacillus calmette-guérin vaccine, Complication, Cutaneous, Diphtheria and pertussis vaccine, Human papilloma virus vaccine, Hepatitis B virus vaccine, Influenza vaccine, Measles, Meningococcal vaccine, Mumps and rubella vaccine, Pneumococcal vaccine, Rash, Skin, Side effect, Tetanus, Vaccine, Varicella vaccine, COVID-19 vaccine.

INTRODUCTION

Vaccination remains the most important and successful public health intervention, as it prevents morbidity and mortality from common infectious diseases. With the increasing number of available and recommended vaccines worldwide, there are

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raising concerns about the potential adverse effects associated with vaccines [1] Vaccines used for achieving immunization against infectious diseases are solutions containing live attenuated pathogens (usually viruses), inactivated whole pathogens, toxoids (an inactivated form of the toxin produced by bacteria that causes the disease), or parts of the pathogens (*e.g*. natural or recombinant proteins, polysaccharides, conjugated polysac- charide or virus-like particles) (Table **1**, modified from Vetter *et al*. 2018) [1 - 3]. They are administered orally, subcutaneously, or intramuscularly. Vaccines are composed of preservatives, adjuvants, antibiotics, stabilizer, and manufacturing by-products in addition to immunogens (bacterial or viral antigens). In various vaccines, egg proteins, gelatin, aluminum hydroxide, aluminum potassium, or aluminum phosphate, thimerosal, 2-phenoxyethanol, formaldehyde, neomycin and/or polyethylene glycol are found seperately or often together (Table **2**) as vaccine constituents [1, 4, 5].

Table 1. Different Types of Vaccines.

Vaccine Types	Examples
Live attenuated vaccines	Measles, mumps, rubella, varicella (*Priorix Tetra, ProQuad*), rotavirus (*Rotarix, Rotavac*), herpes zoster (*Zostavax*), influenza (*Flumist*), oral poliovirus (*OPV*),yellow fever (*Stamaril*), *etc*.
Inactivated vaccines	Whole-cell pertussis (*Tritanrix*), hepatitis A (*Havrix, Vaqta*), rabies (*Rabipur*), tickborne encephalitis (*Encepur*), Japanese encephalitis (*Ixiaro*), cholera (*Dukoral*), COVID-19 vaccine (*Sinovac, Sinopharm, Covaxin*), *etc*.
Split and subunit protein vaccines (natural or recombinant)	Influenza (*Fluarix, Fluarix Tetra, Flulaval, Intanza, Vaxigrip, etc*.), acellular pertussis, hepatitis B (*Engerix B, Recombivax HB*), human papillomavirus (*Cervarix, Gardasil, Gardasil 9*), meningococcal B (*Bexsero, Trumenba*), malaria (*Mosquirix*), herpes zoster (*Shingrix*), COVID-19 vaccine (*Novavax, Soberana*), *etc*.
Toxoid vaccines	Tetanus, diphtheria, acellular pertussis (as part of DTaP combination vaccines: *Boostrix, Infanrix, Adacel, etc*.)
Polysaccharide vaccines	Pneumococcal polysaccharide vaccine (*Pneumovax 23*), meningococcal polysaccharide vaccine (*Mencevax*), *etc*.
Polysaccharide conjugate vaccines	Meningococcal C (*Neisvac*), A (*MenAfriVac*), ACWY (*Nimenrix, Menveo, Menactra*), pneumococcal conjugate vaccine (*Prevnar, Prevnar 13, Synflorix*), Haemophilus influenzae type b (*ACT-HIB*)
Reassortant live attenuated	Rotavirus (*RotaTeq*)
Viral vector DNA vaccines	COVID-19 vaccine (*Sputnik V, Oxford-AstraZeneca, Johnson & Johnson*)
mRNA vaccines	COVID-19 vaccine [*Pfizer (BNT162b2, USA), Moderna (mRNA-1273)*]

Table 2. Vaccine Constituents in Various Vaccines.

Vaccine Constituents	Vaccines
Egg proteins	MMR, influenza, yellow fever, tick-borne encephalitis, rabies vaccines, *etc*.
Gelatin	MMR, Japanese encephalitis virus, varicella, DTaP, *etc*.
Aluminum hydroxide, aluminum potassium, or aluminum phosphate	DTaP, DTaP/poliomyelitis/Haemophilus influenzae, quadrivalent HPV vaccine, hepatitis A, hepatitis B vaccines, *etc*.
Thimerosal	Influenza, DTaP, pneumococcus, meningococcus, hepatitis B, *etc*.
2-phenoxyethanol	DTaP, hepatitis A inactivated and hepatitis B recombinant vaccine, *etc*.
Formaldehyde	Influenza, poliomyelitis, DTaP, hepatitis B vaccine, *etc*.
Neomycin	MMR, DTaP, hepatitis, varicella, influenza, rabies vaccines, *etc*.
Polyethylene glycol	Influenza, hepatitis B, pneumococcal conjugate vaccine, mRNA COVID-19 vaccine, *etc*.

Different vaccines targeting the same pathogen can rely on very different concepts, each having advantages and limitations. Life-long immunity is possible after 1 or 2 doses with live attenuated vaccines that elicit both antibodies and cell-mediated immunity, but they are contraindicated in immunocompromised individuals and pregnant women. While disseminated or prolonged vaccine-strain infections after receiving a live vaccine such as varicella, measles–mumps–rubella (MMR), oral polio or Bacille Calmette–Guérin (BCG) vaccine are exceedingly rare, they are more common complications in immunocompromised populations. The presence of severe T-cell immunodeficiency or a household member with a similar immunodeficiency is therefore an absolute contraindication for immunization with any form of live vaccine. On the other hand, non-live vaccines which contain inactivated whole pathogens or only parts of them such as proteins or polysaccharides (subunit vaccines) generally have a good safety profile even in immunocompromised individuals. However, a major limitation of these vaccines is that their duration of protection tends to be shorter than with live vaccines, and requiring multiple primary and booster doses to achieve long-term immunity. In addition, they have limited immunogenicity and therefore adjuvants are frequently required to improve it [2, 3].

Vaccination against viral and bacterial agents widely performed worldwide is generally safe. Vaccine-associated local or systemic complications may rarely occur ranging from 4.8 to 83 per 100,000 doses of the most frequently used vaccines [1]. Among them cutaneous adverse effects ranging from local (transient pain, tenderness, burning sensations, erythema, swelling, induration, locoregional adenopathy) to generalized skin reactions are very rare compared to the

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