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Collection, compilation and analysis of bacterial vaccines

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ABSTRACT

Background: Bacterial diseases are one of the leading causes of millions of fatalities worldwide, mainly due to antimicrobial resistance. The discovery of chicken cholera vaccine in 1879 revolutionized our fight against bacterial infections. Bacterial vaccines are proven to be highly effective in preventing many infectious diseases. Currently, various licensed vaccines are available against bacterial infections such as typhoid, diphtheria, cholera and tetanus in the market. In this study, we have attempted to compile different information regarding bacterial vaccines, their types, efficacy, mechanism of action, status, route of administration and other relevant details as a knowledgebase known as BacVacDB.

Methods: BacVacDB was implemented using Linux-Apache-MySQL-PHP. HTML, PHP, CSS and Javascript have been used to develop the front end and MySQL for the back end. The data was curated from several sources, including literature, databases and relevant web resources.

Results: This paper reviewed 371 vaccines against 30 human bacterial diseases maintained in BacVacDB, of which 167 are approved and 204 in clinical trials. This database provides the users an effortless search facility in the four modules, 'Search,' 'Browse,' 'External Links' and 'General Information'. In this systematic attempt, we also included the history of vaccines, their mechanism, types, route of administration and approving agencies.

Conclusions: This knowledgebase has an intuitive interface that allows users to explore, search, and download information as well as to submit new bacterial vaccines (https://webs.iiitd.edu.in/raghava/bacvacdb/).

1. Introduction

Host immune response can be activated due to several infections such as pathogenic microbial infections (tuberculosis, typhoid) [1], internal dysfunction of the immune system (autoimmune disorders, cancer) [2] or could be genetically transferred (thalassemia, down syndrome) [3]. Pathogenic microbes like bacteria, fungi, viruses, parasites, protozoans etc., are capable of causing various ailments in the host organisms [4]. These microorganisms can be transmitted through different routes such as air (COVID, whooping cough, mumps), food (salmonellosis, botulism), water (cholera, typhoid fever) or living vectors (AIDS, syphilis) [5].

Bacteria are single-celled organisms that are ubiquitous and have the ability to reproduce on their own [6]. Most (but not all) of the bacteria can be categorized as gram-positive or gram-negative based on the characteristics of the cell wall [7]. Some of their strains are good and beneficial for our body; for instance, those present in the human gastrointestinal tract (*Escherichia coli, Lactobacillus acidophilus* and *Bifidobacterium bifidum*) help in digestion [8]. Whereas few bacterial species can be pathogenic and harmful, causing several infections and diseases [9]. They can infect any organ/part of the human body. *Staphylococcus* and *Streptococcus* bacteria mainly cause skin infections [10]. There are also sexually transmitted bacterial infections such as chlamydia caused by *Chlamydia trachomatis* and gonorrhea by *Neisseria gonorrhoeae* which can infect both men and women [11]. *Neisseria meningitidis* causes meningitis that leads to inflammation of the brain and spinal cord protective membrane, i.e., meninges. Other bacterial species like *Clostridium botulinum* and *Escherichia coli* lead to food-borne diseases or food poisoning due to consuming raw meat, poultry, seafood, and eggs contaminated with bacteria [12]. Most of these bacterial infections are effectively treated using antibiotics.

Antibiotics are substances that can suppress the growth of bacteria

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and are often used for treating most bacterial infections [13]. However, misuse or overuse of antibiotics has resulted in the rapid increase of antibiotic/antimicrobial resistance (AMR) [14]. As per World Health Organization (WHO), AMR has been one of the top 10 threats to human health since many deaths occur due to antimicrobial-resistant pathogens [15]. For example, methicillin-resistant *Staphylococcus aureus* (MRSA), rifampicin-resistant TB (RR-TB) and multi-drug resistant TB (MDR-TB) are the globally identified cases of AMR [16].

Bacterial vaccines can have promising solutions against AMR and help in reducing the burden of infections [15,17]. A vaccine can be defined as antigenic preparation that can elicit the immune response and induce antibody production. Vaccines are available for preventing many human bacterial diseases such as typhoid, diphtheria, cholera and tetanus. Some of the vaccines have completely or nearly eradicated several bacterial infections and provide lifelong protection [17]. There are different types of vaccines that are prepared using distinct processes.

For instance, Bacille Calmette-Guerin (BCG) is a live-attenuated vaccine for pulmonary tuberculosis where the whole bacteria have been weakened [15]. Other examples, such as Vivotif and Typherix, are used to treat typhoid [18]. Toxoids are chemically inactivated toxins and comprise vaccines for diphtheria (Tdvax) [19] and tetanus (Tripedia) [20]. In addition, there are inactivated vaccines, made up of dead bacterial cells inactivated using chemicals, heat or radiation and are used to treat cholera [21], typhoid (Typhim Vi) [22], and Q fever (Q-Vax) [23]. These vaccines are generally administered through different routes such as intramuscular, intradermal, intranasal, intravenous, subcutaneous and oral. Several safety parameters are monitored to assure the safety and quality of vaccines before approval by various regulatory authorities and approving agencies such as the U.S. Food and Drug Administration (FDA) (https://www.fda.gov/) and European Medicines Agency (EMA) (https://www.ema.europa.eu/en).

Moreover, the above information regarding bacterial vaccines, their approval status, and route of administration has been dispersed throughout the literature. Thus, in the present study, we have focused on an in-depth review analysis of different bacterial vaccines, their types, efficacy, mechanism of action, status, route of administration and other important details. The curated information related to bacterial vaccines and diseases is made available in the form of a database named "BacVacDB". We anticipate that this database will be highly beneficial for the pharmaceutical industry and researchers in the development of novel vaccine candidates.

2. Overview of vaccines

2.1. History of vaccines

In 1879, Louis Pasteur developed the first laboratory vaccine for chicken cholera [24], and his experiments spurred the development of live attenuated cholera vaccine and inactivated anthrax vaccine in humans (1897 and 1904, respectively) [25]. Between 1905 and 1918, Albert Calmette and Camille Guerin investigated the mechanism for tuberculosis infection [26]. This led to the discovery of the Bacille-Calmette-Guerin (BCG) vaccine, a live attenuated tuberculosis vaccine that was tested in humans for the first time in 1921 [27] and was first used in new born in 1927 [28]. A live attenuated plague vaccine was reported in 1920 [29]. Alexander Glenny developed a method for inactivating tetanus toxin with formaldehyde in 1923 [30]. Later, the diphtheria toxin was developed in 1926 using the same method [31]. Throughout the 1930s, several vaccines against plague, typhoid, tuberculosis and other diseases were rapidly created. The whole-cell inactivated pertussis vaccine was first approved in the US in 1948 [31]. The first monovalent (group C) meningococcal polysaccharide vaccine was licensed in 1974 [32]. While the pneumococcal polysaccharide vaccine was first licensed for use in the US in 1977, and a 23-valent polysaccharide vaccine (Pneumovax 23, PPSV23) was licensed in 1983 [33]. The quadrivalent groups A, C, Y, and W-135 (Menomune A/C/Y/W-135) meningococcal vaccine was licensed in 1981. In 1985, the first Hib polysaccharide vaccine consisted of the type b purified polysaccharide capsule polyribosylribitol phosphate (PRP) was licensed for use, followed by the conjugate Hib vaccine ProHIBiT in 1987 and PedvaxHIB in 1989 [34,35]. The first conjugate meningococcal vaccine, MCV4 (Menactra), was licensed in 2005 in the United States and a second, MenACWY-CRM (Menveo) licensed in 2010 [36]. In 2015, FDA approved the use of Bexsero, a recombinant vaccine to prevent serogroup B meningococcal disease. Later, Prevnar 20 (pneumococcal 20-valent conjugate vaccine) and Vaxneuvance (pneumococcal 15 valent conjugate vaccine) were approved in 2021 by FDA to prevent invasive pneumococcal disease [37]. The timeline of bacterial vaccine development is depicted in Fig. 1.

2.2. Mechanism of vaccines

Vaccines function by triggering an innate immune response, generating an antigen-specific adaptive immunity [38]. Innate immunity is the first line of barrier against any invading pathogens. The innate immune response is quick, responds within hours after infection and lacks immunologic memory [39]. In contrast, adaptive immunity is the second line of barrier that usually activates when innate immunity fails to destroy a pathogen [39] and plays an essential role in developing immunologic memory. The principal basis of vaccines is to develop long-term immunity in the form of immunological memory after the re-exposure to the same pathogen [40]. It offers immunity by imitating an infection in the body. This infection does not cause any illness and enables the immune system to develop memory T-cells and B lymphocytes. These memory cells elicit the production of antibodies when exposed to the same antigenic strain in the future. The administration of vaccines sometimes can cause mild symptoms like body ache and fever milder than the natural infection necessary for developing immunity [41]. The better insights into the mechanisms of protection mediated by vaccines have been shown in Fig. 2.

2.3. Types of vaccines

Bacterial vaccines can be prepared using different approaches. It may contain a whole pathogenic strain that is killed or inactivated so that it cannot cause any disease (live-attenuated and inactivated vaccines). It may also contain some segments or parts of the pathogen that can elicit the immune response (such as toxoid, subunit and conjugate vaccines). The detailed information for different types of vaccines is described below.

1. **Live attenuated vaccine:** It uses a weakened or attenuated form of the pathogen where attenuation is achieved by creating random or targeted mutations in virulence-related genes [42]. This mutated pathogen cannot cause any disease in the host while inducing a protective immune response. They can rapidly grow in the host and generate continuous antigenic stimulation over time. Some of the live attenuated vaccines include varicella for chickenpox and measles, mumps and rubella (MMR) vaccines [18]. Examples of live attenuated bacterial vaccines include the BCG vaccine developed from the Calmette-Guérin strain of *Mycobacterium bovis*, used for preventing pulmonary tuberculosis [43]. It has been widely used since 1960 and induces trained innate immunity [44]. Vivotif (*Salmonella typhi* Ty21a) is another widely used vaccine against *Salmonella typhi*. Another example is CVD 103-HgR for cholera which is prepared after attenuating *Vibrio cholerae* [18].
2. **Toxoids:** They are chemically inactivated toxins by bacteria like *Clostridium tetani* or *Corynebacterium diphtheria*. Example of toxoid vaccines is Tdvax vaccine for diphtheria and tetanus [45]. In this case, vaccination leads to the formation of antibodies towards these toxins, thereby neutralizing them and preventing serious diseases.

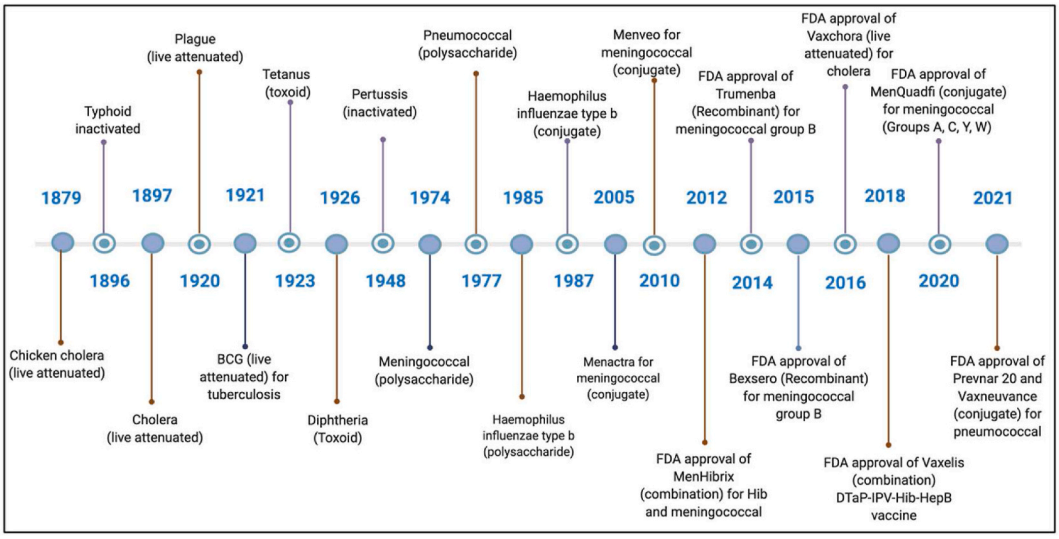

Fig. 1. Timeline of bacterial vaccine development.

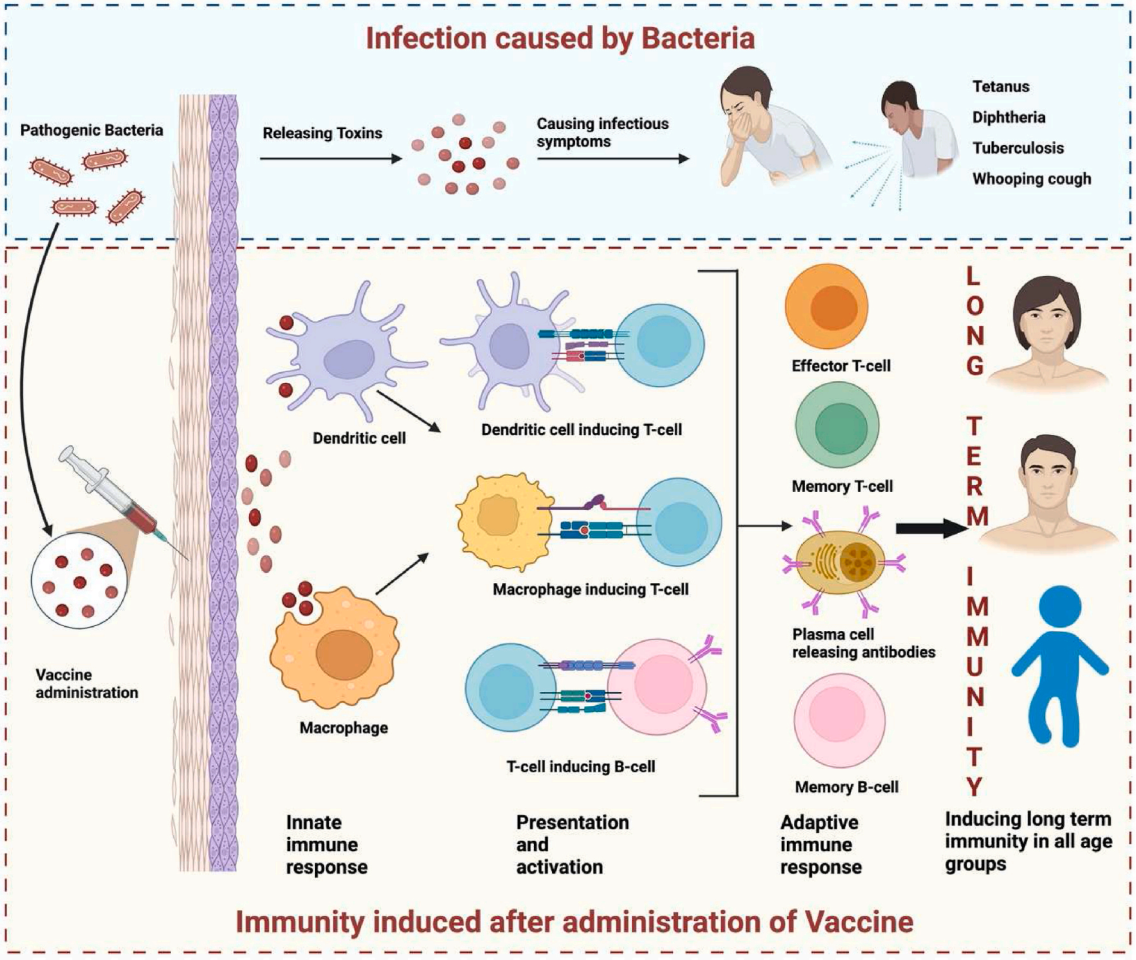

Fig. 2. Representation of the mechanism of vaccines for preventing bacterial diseases and providing long term immunity.

3. **Subunit or polysaccharide vaccine:** They do not contain whole bacteria and use only part of the pathogen, which is sufficient to induce an immune response. It comprises only a single pathogenic antigen and could be administered to people with weakened immune systems. It is prepared by isolating a specific protein from a pathogen and presenting it as an antigen. The immune reaction involves the proteolytic digestion of the ingrained protein, preceded by antigen presentation on major histocompatibility complex (MHC) II. Examples include acellular pertussis vaccine (purified protein subunits),

Haemophilus influenzae type b (Hib) and *Neisseria meningitidis* serogroup B (MenB) subunit vaccine [15].

4. **Conjugate vaccine:** These vaccines are produced using a combination of two different components. A carrier protein is added to the capsular polysaccharide to improve the immune response. Examples are Haemophilus conjugate (HbOC) vaccine, polyribosyl phosphate-T (PRP-T) and polyribosyl phosphate outer membrane protein (PRP-OMP). Other examples are the meningococcal vaccine, which covers the serogroups A, C, W-135, and Y serotypes [42]. With the implementation of pneumococcal conjugate vaccines (PCV) in low-income countries, vaccination has prevented approximately 500,000 childhood deaths [46].
5. **Inactivated or killed vaccine:** It contains whole bacteria and bacterial cells that have been inactivated using heat or chemicals. For example, Dukoral is a killed vaccine used for cholera [47] and Plague vaccine USP for plague [48].
6. **Recombinant vaccine:** These are the novel vaccination strategies using live attenuated bacteria as vectors of recombinant genes. These vaccines are developed since they are more efficient, less reactive and offer wider protection against various serotypes of a bacterium [42]. Examples include Bexsero [49] and Trumenba [50] vaccines for preventing meningococcal disease.
7. **Genetic or Gene-based vaccine:** It contains the nucleic acids (DNA or RNA) that involve the transfer of a gene sequence encoding an antigen into host cells. The host cells can elicit an immune response against this antigen for treating disease [51]. Currently, there is no approved gene-based vaccine for humans against bacterial diseases.
8. **Viral vector-based vaccine:** Viral vectors use the modified version of the virus, which is harmless and activates the immune system to fight against the infection [52]. Examples include TB/FLU-01L tuberculosis vaccine (phase 1 clinical trial) containing replication-deficient recombinant influenza virus A expressing ESAT-6 antigen [53], NasoShield (adenovirus-vectored anthrax vaccine) [54].
9. **Combination vaccine:** It is also known as polyvalent vaccine. It combines two or more vaccines that could be administered separately into a single dose. They are different from monovalent vaccines as they can provide immunity against more than one type of micro-organisms, whereas monovalent vaccines immunize against a single antigen or pathogen [55]. It also leads to fewer injections and reduces the cost of healthcare visits. Some of the combination vaccines for bacterial infections include DTap, Tdap, Dt, and TD, which are used to prevent multiple diseases like diphtheria, tetanus, and pertussis [56]. Table 1 shows the description of several types of vaccines along with their pros and cons and the relevant examples.

2.4. Administration of vaccines

The administration route refers to the path by which a vaccine is administered or brought in contact with the body [62]. Vaccines can be administered via invasive and non-invasive routes. Invasive routes include intramuscular, intradermal, intravenous and subcutaneous. Whereas non-invasive routes like oral and intranasal are needle-less and more favourable [63].

(a) **Intramuscular**: It means delivering the vaccine into the muscle mass. Most of the bacterial vaccines containing adjuvants are administered intramuscularly to eliminate the adverse local effects. For example, Synflorix [64] vaccine for pneumococcal and VLA15 [65] for Lyme disease are delivered intramuscularly.
(b) **Subcutaneous**: A vaccine is injected into the subcutaneous layer of the skin. Examples are the PBT vaccine [66] for botulism and Spirolept vaccine [67] for Leptospirosis.
(c) **Intradermal**: A vaccine is directly delivered in the dermis (upper layer of the skin). VPM1002 [68] and Immuvac vaccines for pulmonary tuberculosis are given intradermally [69].
(d) **Intranasal**: This is a needle-free approach through the nasal mucosa. For example, Invaplex 50 vaccine against bacillary dysentery (shigellosis) [70] and BW-1010 recombinant vaccine for anthrax is administered via intranasal route.
(e) **Oral**: A vaccine is given orally, thus eliminating the need for a needle or syringe. It is easy to manage and does not require special skills [63]. Vaxchora vaccine to prevent cholera and

Table 1
Detailed information about different types of vaccines used for preventing human bacterial infections.

Vaccine Type	Description	Pros	Cons	Examples
Live attenuated (LAVs)	Weakened or attenuated form of the pathogen	- Strong immune response - Easy to manufacture	- Poor stability and difficult maintenance - Not suitable for people with compromised immune systems	BCG (pulmonary tuberculosis) [44], Vivotif (typhoid), CVD 103-HgR (cholera) [18]
Toxoids	Chemically inactivated toxins by bacteria	- Safe for immunocompromised individuals - Stable and long lasting	- Several doses and adjuvant required - Local reactions more common	Tdvax (diphtheria and tetanus) [19], BAT (botulism) [57]
Subunit or polysaccharide	Contains specific parts of the pathogen	- Safe and stable vaccines - No live components	- Multiple doses and adjuvant required. - Complex to manufacture	Pneumovax 23 (pneumococcal) Mencevax ACWY (meningococcal)
Conjugate	Combination of two different components	- Safe and reliable - Strong immune response for very young children	- High cost - Carrier proteins can induce non-specific immune response	MenHibrix (Hib and meningococcal) [58], Prevnar 20 (pneumococcal)
Inactivated or killed	Contains whole killed bacteria	- No risk and given to immunocompromised people - Easy to store and ship	- Less robust response - Multiple doses or booster shots required	Dukoral (cholera) [47], Plague vaccine USP (plague) [48]
Recombinant	Based on recombinant DNA technology	- Easily produced at large scale - Involves less risk	Adjuvant required	Bexsero (meningococcal) [49], Trumenba (meningococcal) [50]
Genetic (or Gene-based) vaccine	Contains DNA/RNA to elicit an immune response	- Triggers all components of the immune system for better protection - Safe and inexpensive to produce	- May affect the normal cell functioning by integrating into the human genome	GX-70 [59]
Viral vector-based vaccine	Contains modified virus as a vector	- Induces robust cytotoxic T lymphocyte (CTL) response - Enhance immunogenicity without an adjuvant	- Previous exposure to the vector could result in reduced effectiveness - Complex manufacturing process	TB/FLU-01L [53], NasoShield [54]
Combination vaccine	Provides immunity against two or more antigens	- Reduces the number of doses and visits to doctor - Increased immunization compliance	- Sometimes result into more pain or swelling - Not clear which component is responsible for a particular adverse effect	Pediarix [60], Infanrix-hexa [61]

CDVAX vaccine for *Clostridium difficile* infection are given orally [71].

2.5. BacVacDB: a database of bacterial vaccines

Bacterial vaccines are important in preventing human diseases caused by harmful strains of bacteria such as tuberculosis, typhoid, cholera etc. There are a number of bacterial vaccines already in use, as well as vaccines undergoing human clinical trials. In this study, we have curated comprehensive information for bacterial vaccines and diseases to serve the scientific community. All this information is made freely available in the form of a web resource, BacVacDB. This database holds important details about the vaccines, such as their name, types, dosage formulation, and mechanism of action on a single platform to save time and be accessed from https://webs.iiitd.edu.in/raghava/bacvacdb/.

3. Materials and methods

3.1. Data collection and curation

There is a variety of relevant information regarding the bacterial vaccines used for preventing different diseases, which is scattered in different forms like literature, databases and web resources. BacVacDB database was created by manually curating the information obtained from Google search engine using different terms relevant to bacteria and its associated vaccines. Other important information is also retrieved from reliable websites like US FDA (https://www.fda.gov), WHO (https://www.who.int), Centers for Disease Control and Prevention (https://www.cdc.gov), Electronic medicines compendium (https://www.medicines.org.uk/emc/), and ClinicalTrials.gov (https://clinicaltrials.gov/).

3.2. Database architecture and web interface

BacVacDB database has been built using a standard platform on the Linux-Apache-MySQL-PHP (LAMP). MySQL (version 5.7.31) for managing the data and Apache (version 2.4.46) as HTTP server were used for designing this database. HTML (version 5), PHP (version 7.3.21), CSS (version 3) and Javascript (version 1.8) have been used for developing responsive front ends which are compatible with smartphones, tablets and desktops and MySQL has been used for creating the back end. PHP programming language was used to develop a common interface. The complete architecture of this database is explained in Fig. 3.

3.3. Web server facility

BacVacDB web server is a freely available server built in order to serve the community. It provides vast information about the vaccines for human bacterial diseases on a single platform. There are four major modules included in the webserver for an effortless search facility i.e., 'Search,' 'Browse,' 'External Links' and 'General Information'.

Search – Under this module, basic and advanced search options have been implemented.

Basic search: The basic search option helps to search in any field or against multiple fields. By default, this module explores major fields like vaccine name, disease, bacteria, administration route or vaccine type.

Advanced search: Advanced query is a more complex search where the user can give different queries simultaneously with the help of other boolean operators (like AND, OR and NOT) and receive the output accordingly. These search options allow users to download the displayed entries in comma-separated format.

Browse - This facility allows the user to browse data with respect to different fields like (i) Bacterial disease - this option displays a table

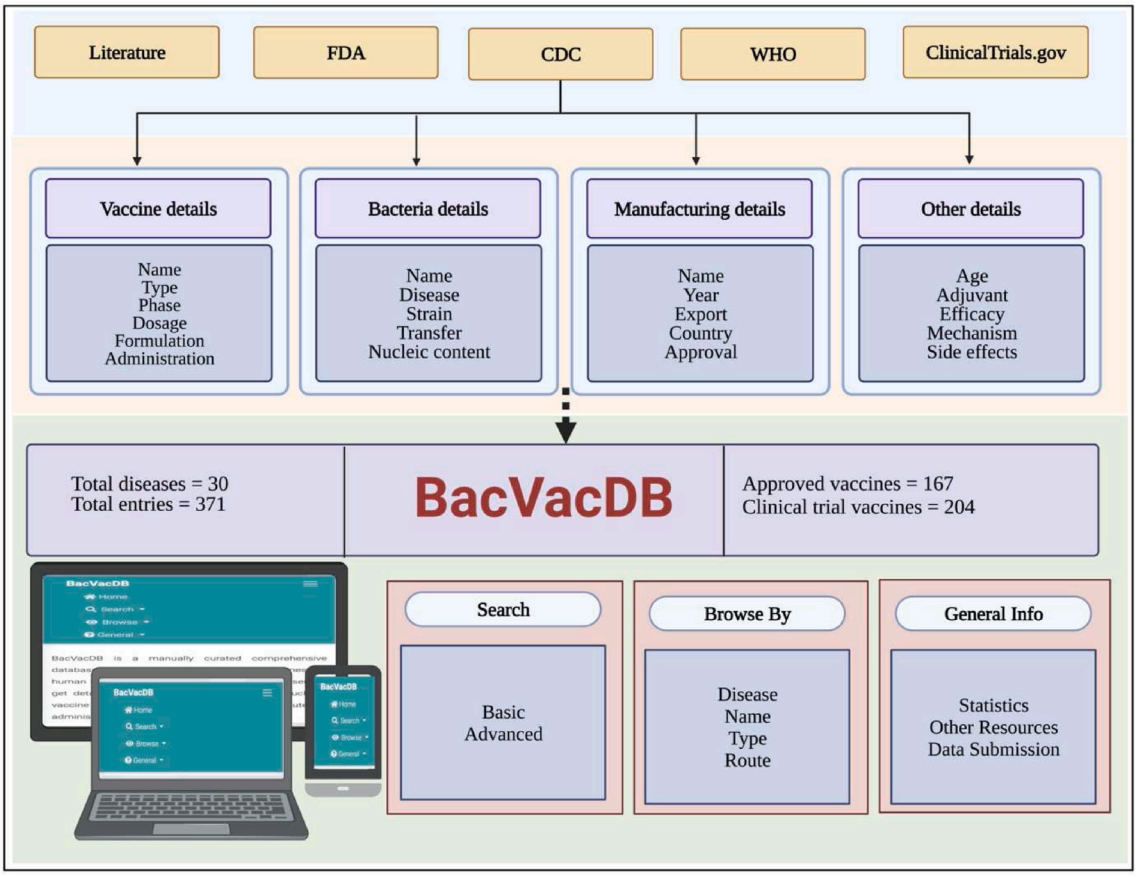

Fig. 3. Schematic representation of BacVacDB architecture and its modules.

showing several bacterial disease names and their corresponding vaccine count, (ii) Bacteria name - displays different bacteria names and their vaccine counts, (iii) Vaccine type - shows multiple types of vaccines and their counts and (iv) Vaccine route of administration - helps in browsing vaccines as per their route of administration or site.

External Links - In this module, we are cross-linking our database BacVacDB to other well-established databases such as DrugBank (https://go.drugbank.com/) [72], Therapeutic Target Database (TTD) (http://db.idrblab.net/ttd/) [73], Malacards (https://www.malacards.org/) [74], Swiss-Prot (https://www.uniprot.org/) [75] and NCBI (https://www.ncbi.nlm.nih.gov/) that are widely used. This module has different fields, namely Disease information, Adjuvants information and Other resources. Disease information displays a table showing several bacterial diseases, their causative agents, along with other information such as proteome ID for the causative agent link to Swiss-Prot, taxonomy link to NCBI, drug information from DrugBank, therapeutic target information from TTD and disease-specific information from MalaCards. Moreover, Adjuvant information displays different adjuvants for bacterial vaccines, its description and other additional links to DrugBank, Ontobee (https://ontobee.org) [76] and PubChem (https://pubchem.ncbi.nlm.nih.gov/). Other resources field provides additional websites and resources available for vaccine information.

General Information- This module emphasises on general information about the database. It includes (i) statistics shows the graphical representation of bacterial diseases, approved vaccines, vaccines types and route of administration (ii) data submission page, allows user to submit the data for any other human bacterial vaccine (iii) help page to assist user about the utility of different modules. Fig. 4 illustrating the major modules of the webserver.

4. Results

4.1. Data analysis and statistics

The current version of BacVacDB holds 371 vaccine entries for 30 human bacterial diseases extracted from literature, websites and existing databases. Among the 371 entries, 167 entries are for approved vaccines, while 204 are in different phases of human clinical trials. All the curated information regarding the human bacterial vaccines is catalogued in 33 various fields of the table. This freely available database contains vast information related to the vaccines like their name, type, age range, description, manufacturer name, manufacturing country, year of manufacture, phase (approved or clinical), efficacy, form of presentation, dosage, mechanism of action, administration route, indication, export, approval agency, adjuvant (if any), repurposing, side effects, post-vaccination and dose type. It also contains information about the bacteria causing a particular disease, like the bacteria name, disease name, its nucleic acid content, and its strain.

The distribution of vaccines for various diseases is depicted in Fig. 5A. There are 66 vaccine entries for diphtheria cover around 22% of vaccines, 20% of vaccines belong to tetanus (lockjaw) and 15% for pertussis (whooping cough). We found that majority of the vaccine is used for preventing diphtheria, tetanus and pertussis.

Fig. 5B depicts the number of approved vaccines for different bacterial diseases. Among them, 36 are for tetanus, followed by diphtheria (35), pertussis (26), and other diseases.

Fig. 5C represents the various types of vaccines. Out of which, combination vaccines are majorly present (131), and the remaining include conjugate (64), inactivated (56), recombinant (31) and others.

Fig. 5D shows the distribution of vaccines with respect to their route of administration. It has been observed that the majority of the vaccines (260) are administered intramuscularly, 37 are given orally, and 26 subcutaneously followed by others.

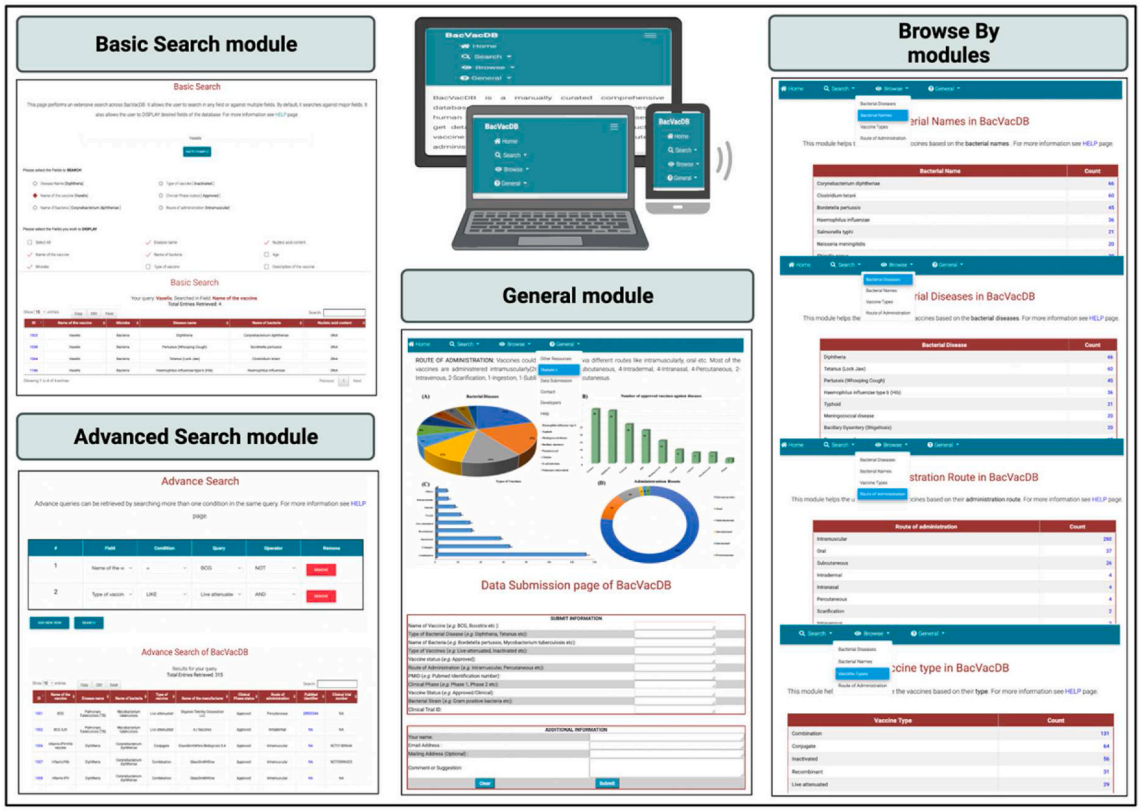

Fig. 4. Pictorial representation of the major modules of the webserver BacVacDB.

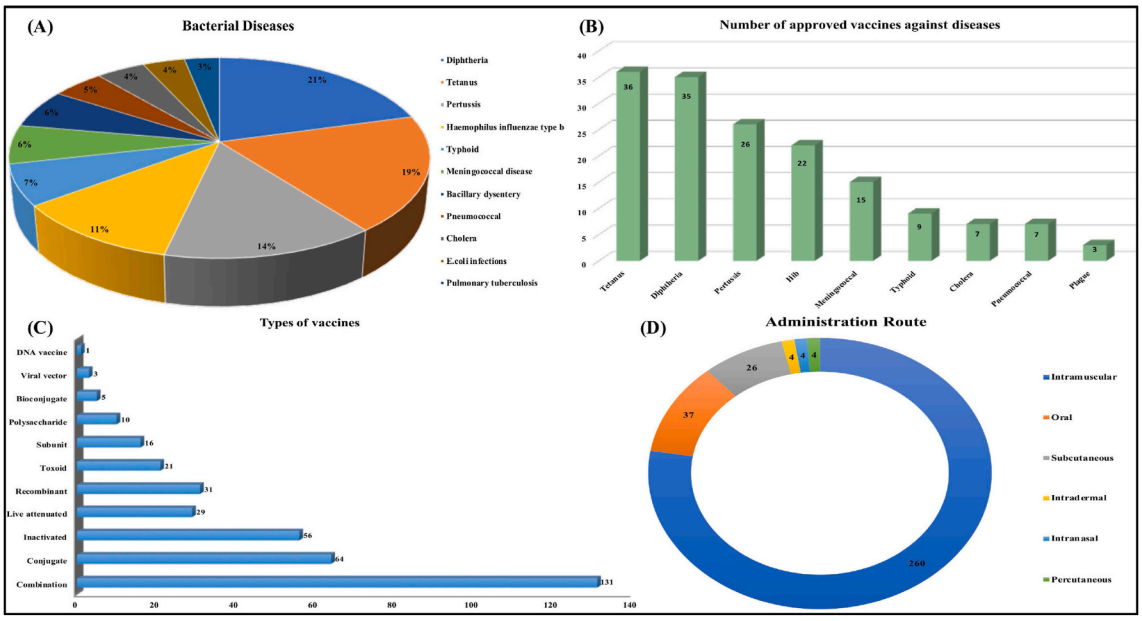

Fig. 5. Depiction of vaccine entries in BacVacDB based on (a) bacterial diseases in humans (b) number of approved vaccines, (c) types of vaccines, and (d) administration route.

4.2. Comparison with existing methods

BacVacDB is the first database solely dedicated to bacterial vaccines for human use. It comprises 371 human vaccines for 30 bacterial diseases, which is a piece of vast information compared to other databases such as Vaccine Investigation and Online Information Network (VIOLIN) (http://www.violinet.org/). The Vaxquery component of the VIOLIN database majorly contains several vaccines licensed for animals (monkeys, pigs, cattle). This database covers around 135 vaccines against 16 human bacterial diseases. Huvax (https://www.violinet.org/huvax/), another component of VIOLIN database, is a web based licensed human vaccine database that only contains 110 licensed vaccines for 12 bacterial diseases. Another knowledgebase, Vaccine Knowledge Project (https://vk.ovg.ox.ac.uk/vk/), managed by Oxford Vaccine Group, contains approximately 31 vaccines for 7 human bacterial diseases. Therefore, in this study, we have made an attempt to compile all the relevant information on the bacterial vaccines for treating diseases in humans. We have collated all the details on a single platform in the form of a database named "BacVacDB". Along with vaccines, other information like year of manufacture, the form of presentation, approval, repurposing, post-vaccination, and dose type is also incorporated. The comparison of BacVacDB with other vaccine databases is tabulated in Table 2.

4.3. Usefulness of BacVacDB

BacVacDB can be employed to extract detailed information regarding any bacterial vaccines for humans on a single platform. Fig. 6 demonstrates the steps for the users to fetch the relevant information from the database. For instance, if a user wants to search for a vaccine named 'Vaxelis', which can be used to treat several types of bacterial diseases, the user should type Vaxelis into the search box provided on the basic search page and can select other options as per desired (Fig. 6A and B). By clicking on the search button, the result page will be displayed (Fig. 6C) along with the other selected fields. Each entry is specified with a unique ID which is hyperlinked with the bacterial vaccine card that gives comprehensive information about each vaccine (Fig. 6D).

Table 2
Comparison of BacVacDB with other vaccine databases.

Database	Description (Link)	Number of vaccines	Number of human bacterial diseases
BacVacDB	A manually curated comprehensive database for vaccines related to human bacterial diseases (https://webs.iiitd.edu.in/raghava/bacvacdb/)	371	30
Vaxquery	Mainly contain vaccines licensed for animals and covers some of the vaccines for humans (https://www.violinet.org/vaxquery/)	135	16
Huvax	Web-based human licensed vaccine database (https://www.violinet.org/huvax/)	110	12
Vaccine Knowledge Project	A knowledge base of vaccines for infectious diseases caused by bacteria and viruses (https://vk.ovg.ox.ac.uk/vk/)	31	7

5. Discussion & conclusion

One of the most significant concerns of the 21st century is the prevention and treatment of bacterial infections. Bacteria are known to cause several deadly infectious diseases in humans, such as tuberculosis, cholera, tetanus and pneumonia. Antibiotics are prescribed by doctors for treating different bacterial diseases since they help in suppressing the growth of the bacteria. Overuse or misuse of antibiotics could make the bacteria resistant, which is dangerous for human health. The development of bacterial vaccines can be proven solutions to combat the emergence of AMR. They play an important role in saving our lives and help in preventing the critical diseases caused by harmful strains of bacteria. Vaccine development is a complex process and requires multiple clinical testing rounds to ensure that the vaccine is safe and effective to be used for humans [77]. Several regulatory authorities ensure that vaccines used worldwide are safe, potent, and of good

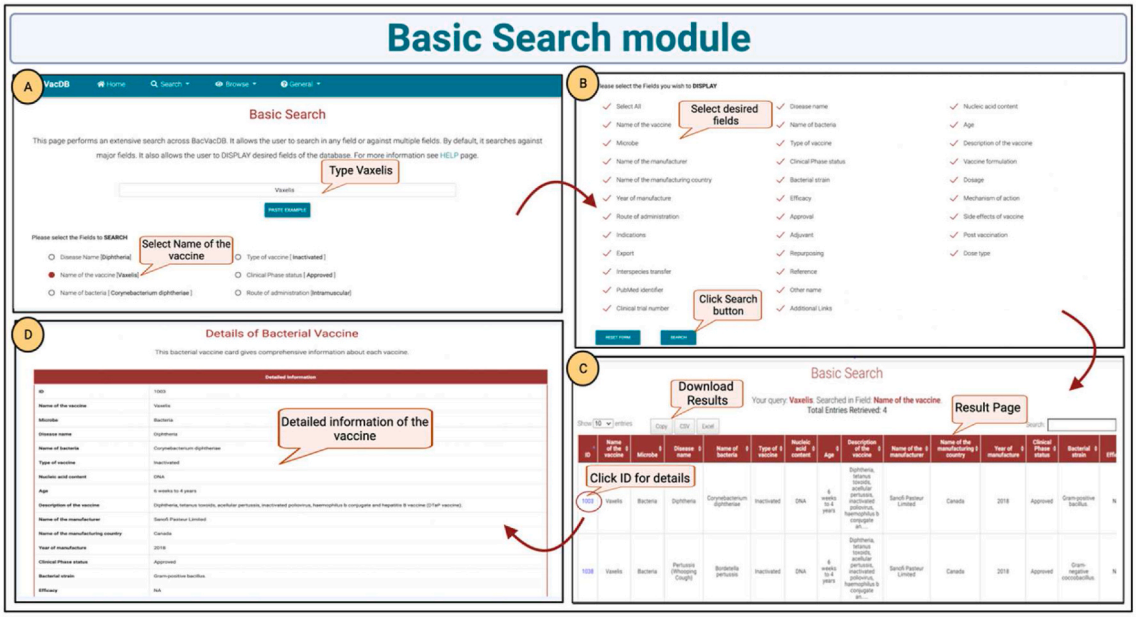

Fig. 6. (A) Screenshot of BacVacDB showing the submission of a query on basic search page. (B) Showing the other fields to be displayed (C) Result page after submission of a query in the basic search page (D) Displaying the detailed information page after the result page.

quality. The U.S. FDA, National regulatory authorities (NRA) or Pharmacovigilance centers (NPCs) [78], Center for Biologics Evaluation and Research (CBER) [79], European Medicines Agency and Central Drugs Standard Control Organization (CDSCO) under the Directorate General of Health Services, Ministry of Health & Family Welfare (https://cdsco.gov.in/opencms/opencms/en/Home/) are the regulatory bodies.

Since the bacterial vaccine information is scattered in different forms, it would be great help if all the information related to bacterial vaccines and their corresponding microorganism (bacteria) could be accessed from a single platform by the scientific community or general public to save their time and effort. Taking this perspective into consideration, BacVacDB database was designed a web-based platform containing massive information related to bacterial vaccines for human use. It is a user-friendly interface incorporating 371 vaccine entries for 30 human bacterial diseases, where 167 entries are for approved vaccines and 204 vaccines in clinical trials. All the comprehensive information can be accessed from the user-friendly interface, available at https://webs.iiitd.edu.in/raghava/bacvacdb/. We believe that this database will be beneficial for the scientific community and the general public.

5.1. Limitations and future directions

We made every effort to serve the research community by providing all the information on bacterial vaccines from the available resources. However, one of the limitations of our database is that the information regarding the vaccine targets of the bacteria has not been included. Another limitation is that we have only covered the data related to bacterial vaccines against humans and not for other hosts (such as mice and monkeys). Even though we have manually curated the data and scrupulously verified it to reduce the risk of error, there may be the possibility of biases due to human errors. We will make every effort to update the database on a regular basis, preferably every year. Moreover, we will try to include and update vaccines which are either approved or under clinical trials.

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Author contributions

SG manually collected and curated all the data. SG, NS and NLD analysed the data. SG, NLD, NS and SJ developed the web interface. SG, NS, NLD, SJ and GPSR wrote the manuscript. GPSR conceived and coordinated the project and provided overall supervision. All authors have read and approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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