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Vaccines and Their Significance

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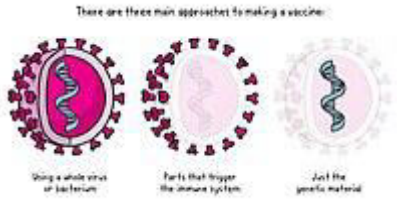
ABSTRACT: A vaccine is a biological preparation that provides active acquired immunity to a particular infectious or malignant disease.[1][2] The safety and effectiveness of vaccines has been widely studied and verified.[3][4] A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and recognize further and destroy any of the microorganisms associated with that agent that it may encounter in the future.

KEYWORDS-vaccine, immunization, disease, microbes, immunity, proteins

I.INTRODUCTION

Types



Vaccines typically contain attenuated, inactivated or dead organisms or purified products derived from them. There are several types of vaccines in use.[55] These represent different strategies used to try to reduce the risk of illness while retaining the ability to induce a beneficial immune response.

Attenuated

Some vaccines contain live, attenuated microorganisms. Many of these are active viruses that have been cultivated under conditions that disable their virulent properties, or that use closely related but less dangerous organisms to produce a broad immune response. Although most attenuated vaccines are viral, some are bacterial in nature. Examples include the viral diseases yellow fever, measles, mumps, and rubella, and the bacterial disease typhoid. The live Mycobacterium tuberculosis vaccine developed by Calmette and Guérin is not made of a contagious strain but contains a virulently modified strain called "BCG" used to elicit an immune response to the vaccine. The live attenuated vaccine containing strain Yersinia pestis EV is used for plague immunization. Attenuated vaccines have some advantages and disadvantages. Attenuated, or live, weakened, vaccines typically provoke more durable immunological responses. But they may not be safe for use in immunocompromised individuals, and on rare occasions mutate to a virulent form and cause disease.[56]

Inactivated[1,2,3]

Some vaccines contain inactivated, but previously virulent, micro-organisms that have been destroyed with chemicals, heat, or radiation[57] – "ghosts", with intact but empty bacterial cell envelopes. They are considered an intermediate phase between the inactivated and attenuated vaccines.[58] Examples include IPV (polio vaccine), hepatitis A vaccine, rabies vaccine and most influenza vaccines.[59]

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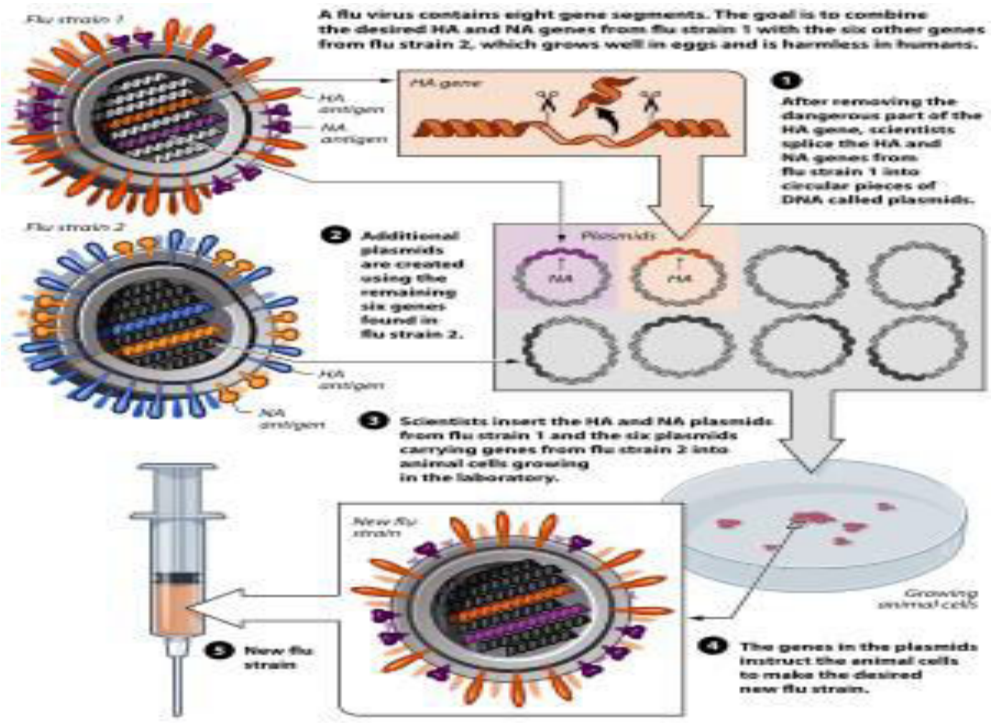

Avian flu vaccine development by reverse genetics techniques

Toxoid

Toxoid vaccines are made from inactivated toxic compounds that cause illness rather than the micro-organism.[59] Examples of toxoid-based vaccines include tetanus and diphtheria.[59] Not all toxoids are for micro-organisms; for example, Crotalus atrox toxoid is used to vaccinate dogs against rattlesnake bites.[60]

Subunit

Rather than introducing an inactivated or attenuated micro-organism to an immune system (which would constitute a "whole-agent" vaccine), a subunit vaccine uses a fragment of it to create an immune response. One example is the subunit vaccine against hepatitis B, which is composed of only the surface proteins of the virus (previously extracted from the blood serum of chronically infected patients but now produced by recombination of the viral genes into yeast).[61] Another example is edible algae vaccines, such as the virus-like particle (VLP) vaccine against human papillomavirus (HPV), which is composed of the viral major capsid protein.[62] Another example is the hemagglutinin and neuraminidase subunits of the influenza virus.[59] A subunit vaccine is being used for plague immunization.[63]

Conjugate

Certain bacteria have a polysaccharide outer coat that is poorly immunogenic. By linking these outer coats to proteins (e.g., toxins), the immune system can be led to recognize the polysaccharide as if it were a protein antigen. This approach is used in the Haemophilus influenzae type B vaccine.[64]

Outer membrane vesicle

Outer membrane vesicles (OMVs) are naturally immunogenic and can be manipulated to produce potent vaccines. The best known OMV vaccines are those developed for serotype B meningococcal disease.[65][66]

Heterotypic

Heterologous vaccines also known as "Jennerian vaccines", are vaccines that are pathogens of other animals that either do not cause disease or cause mild disease in the organism being treated. The classic example is Jenner's use of cowpox to protect against smallpox. A current example is the use of BCG vaccine made from Mycobacterium bovis to protect against tuberculosis.[67]

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Genetic vaccine

Genetic vaccines are based on the principle of uptake of a nucleic acid into cells, whereupon a protein is produced according to the nucleic acid template. This protein is usually the immunodominant antigen of the pathogen or a surface protein that enables the formation of neutralizing antibodies. The subgroup of genetic vaccines encompass viral vector vaccines, RNA vaccines and DNA vaccines.[citation needed]

Viral vector

Viral vector vaccines use a safe virus to insert pathogen genes in the body to produce specific antigens, such as surface proteins, to stimulate an immune response.[68][69]

RNA

An mRNA vaccine (or RNA vaccine) is a novel type of vaccine which is composed of the nucleic acid RNA, packaged within a vector such as lipid nanoparticles.[70] Among the COVID-19 vaccines are a number of RNA vaccines to combat the COVID-19 pandemic and some have been approved or have received emergency use authorization in some countries. For example, the Pfizer-BioNTech vaccine and Moderna mRNA vaccine are approved for use in adults and children in the US.[71][72][73]

DNA

A DNA vaccine uses a DNA plasmid (pDNA)) that encodes for an antigenic protein originating from the pathogen upon which the vaccine will be targeted. pDNA is inexpensive, stable, and relatively safe, making it an excellent option for vaccine delivery.[74]

This approach offers a number of potential advantages over traditional approaches, including the stimulation of both B- and T-cell responses, improved vaccine stability, the absence of any infectious agent and the relative ease of large-scale manufacture.[75]

Experimental

Many innovative vaccines are also in development and use.

- Dendritic cell vaccines combine dendritic cells with antigens to present the antigens to the body's white blood cells, thus stimulating an immune reaction. These vaccines have shown some positive preliminary results for treating brain tumors[76] and are also tested in malignant melanoma.[77]
- Recombinant vector – by combining the physiology of one micro-organism and the DNA of another, immunity can be created against diseases that have complex infection processes. An example is the RVSV-ZEBOV vaccine licensed to Merck that is being used in 2018 to combat ebola in Congo.[78]
- T-cell receptor peptide vaccines are under development for several diseases using models of Valley Fever, stomatitis, and atopic dermatitis. These peptides have been shown to modulate cytokine production and improve cell-mediated immunity.
- Targeting of identified bacterial proteins that are involved in complement inhibition would neutralize the key bacterial virulence mechanism.[79]
- The use of plasmids has been validated in preclinical studies as a protective vaccine strategy for cancer and infectious diseases. However, in human studies, this approach has failed to provide clinically relevant benefit. The overall efficacy of plasmid DNA immunization depends on increasing the plasmid's immunogenicity while also correcting for factors involved in the specific activation of immune effector cells[4,5,6]
- Bacterial vector – Similar in principle to viral vector vaccines, but using bacteria instead.[65]
- Antigen-presenting cell[65]

While most vaccines are created using inactivated or attenuated compounds from micro-organisms, synthetic vaccines are composed mainly or wholly of synthetic peptides, carbohydrates, or antigens.

Valence

Vaccines may be monovalent (also called univalent) or multivalent (also called polyvalent). A monovalent vaccine is designed to immunize against a single antigen or single microorganism.[81] A multivalent or polyvalent vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms.[82] The valency of a multivalent vaccine may be denoted with a Greek or Latin prefix (e.g., bivalent, trivalent, or tetravalent/quadrivalent). In certain cases, a monovalent vaccine may be preferable for rapidly developing a strong immune response.[83]

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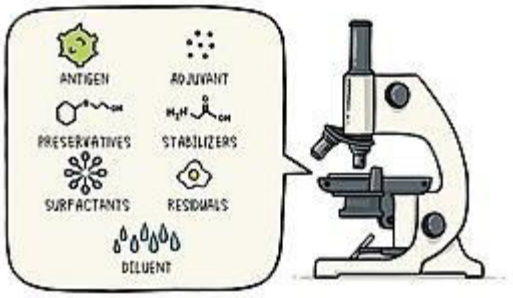
Interactions

When two or more vaccines are mixed in the same formulation, the two vaccines can interfere. This most frequently occurs with live attenuated vaccines, where one of the vaccine components is more robust than the others and suppresses the growth and immune response to the other components.[84]

This phenomenon was first[when?] noted in the trivalent Sabin polio vaccine, where the amount of serotype 2 virus in the vaccine had to be reduced to stop it from interfering with the "take" of the serotype 1 and 3 viruses in the vaccine.[85] It was also noted in a 2001 study to be a problem with dengue vaccines, where the DEN-3 serotype was found to predominate and suppress the response to DEN-1, -2 and -4 serotypes.[86]

Other contents[7,8,9]



Graphic from the World Health Organization describing the main ingredients typically in vaccinesA vaccine dose contains many ingredients (stabilizers, adjuvants, residual inactivating ingredients, residual cell culture materials, residual antibiotics and preservatives) very little of which is the active ingredient, the immunogen. A single dose may have merely nanograms of virus particles, or micrograms of bacterial polysaccharides. A vaccine injection, oral drops or nasal spray is mostly water. Other ingredients are added to boost the immune response, to ensure safety or help with storage, and a tiny amount of material is left-over from the manufacturing process. Very rarely, these materials can cause an allergic reaction in people who are very sensitive to them.

Adjuvants

Vaccines typically contain one or more adjuvants, used to boost the immune response. Tetanus toxoid, for instance, is usually adsorbed onto alum. This presents the antigen in such a way as to produce a greater action than the simple aqueous tetanus toxoid. People who have an adverse reaction to adsorbed tetanus toxoid may be given the simple vaccine when the time comes for a booster.[87]

In the preparation for the 1990 Persian Gulf campaign, the whole cell pertussis vaccine was used as an adjuvant for anthrax vaccine. This produces a more rapid immune response than giving only the anthrax vaccine, which is of some benefit if exposure might be imminent.[88]

Preservatives

Vaccines may also contain preservatives to prevent contamination with bacteria or fungi. Until recent years, the preservative thiomersal (a.k.a. Thimerosal in the US and Japan) was used in many vaccines that did not contain live viruses. As of 2005, the only childhood vaccine in the U.S. that contains thiomersal in greater than trace amounts is the influenza vaccine,[89] which is currently recommended only for children with certain risk factors.[90] Single-dose influenza vaccines supplied in the UK do not list thiomersal in the ingredients. Preservatives may be used at various stages of the production of vaccines, and the most sophisticated methods of measurement might detect traces of them in the finished product, as they may in the environment and population as a whole.[91]

Many vaccines need preservatives to prevent serious adverse effects such as Staphylococcus infection, which in one 1928 incident killed 12 of 21 children inoculated with a diphtheria vaccine that lacked a preservative.[92] Several preservatives are available, including thiomersal, phenoxyethanol, and formaldehyde. Thiomersal is more effective against bacteria, has a better shelf-life, and improves vaccine stability, potency, and safety; but, in the U.S., the European Union, and a few other affluent countries, it is no longer used as a preservative in childhood vaccines, as a precautionary measure due to its mercury content.[93] Although controversial claims have been made that thiomersal contributes to autism, no convincing scientific evidence supports these claims.[94] Furthermore, a 10–11-year study of 657,461 children found that the MMR vaccine does not cause autism and actually reduced the risk of autism by seven percent.[95][96]

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Excipients

Beside the active vaccine itself, the following excipients and residual manufacturing compounds are present or may be present in vaccine preparations:[97]

- Aluminum salts or gels are added as adjuvants. Adjuvants are added to promote an earlier, more potent response, and more persistent immune response to the vaccine; they allow for a lower vaccine dosage.
- Antibiotics are added to some vaccines to prevent the growth of bacteria during production and storage of the vaccine.
- Egg protein is present in the influenza vaccine and yellow fever vaccine as they are prepared using chicken eggs. Other proteins may be present.
- Formaldehyde is used to inactivate bacterial products for toxoid vaccines. Formaldehyde is also used to inactivate unwanted viruses and kill bacteria that might contaminate the vaccine during production.
- Monosodium glutamate (MSG) and 2-phenoxyethanol are used as stabilizers in a few vaccines to help the vaccine remain unchanged when the vaccine is exposed to heat, light, acidity, or humidity.[10,11,12]
- Thiomersal is a mercury-containing antimicrobial that is added to vials of vaccines that contain more than one dose to prevent contamination and growth of potentially harmful bacteria. Due to the controversy surrounding thiomersal, it has been removed from most vaccines except multi-use influenza, where it was reduced to levels so that a single dose contained less than a microgram of mercury, a level similar to eating ten grams of canned tuna.[98]

DISCUSSION

Vaccine production is fundamentally different from other kinds of manufacturing – including regular pharmaceutical manufacturing – in that vaccines are intended to be administered to millions of people of whom the vast majority are perfectly healthy.[125] This fact drives an extraordinarily rigorous production process with strict compliance requirements that go far beyond what is required of other products.[125]

Depending upon the antigen, it can cost anywhere from US$50 to $500 million to build a vaccine production facility, which requires highly specialized equipment, clean rooms, and containment rooms.[126] There is a global scarcity of personnel with the right combination of skills, expertise, knowledge, competence and personality to staff vaccine production lines.[126] With the notable exceptions of Brazil, China, and India, many developing countries' educational systems are unable to provide enough qualified candidates, and vaccine makers based in such countries must hire expatriate personnel to keep production going.[126]

Vaccine production has several stages. First, the antigen itself is generated. Viruses are grown either on primary cells such as chicken eggs (e.g., for influenza) or on continuous cell lines such as cultured human cells (e.g., for hepatitis A).[127] Bacteria are grown in bioreactors (e.g., Haemophilus influenzae type b). Likewise, a recombinant protein derived from the viruses or bacteria can be generated in yeast, bacteria, or cell cultures.[128][129]

After the antigen is generated, it is isolated from the cells used to generate it. A virus may need to be inactivated, possibly with no further purification required. Recombinant proteins need many operations involving ultrafiltration and column chromatography. Finally, the vaccine is formulated by adding adjuvant, stabilizers, and preservatives as needed. The adjuvant enhances the immune response to the antigen, stabilizers increase the storage life, and preservatives allow the use of multidose vials.[128][129] Combination vaccines are harder to develop and produce, because of potential incompatibilities and interactions among the antigens and other ingredients involved.[130]

The final stage in vaccine manufacture before distribution is fill and finish, which is the process of filling vials with vaccines and packaging them for distribution. Although this is a conceptually simple part of the vaccine manufacture process, it is often a bottleneck in the process of distributing and administering vaccines.[131][132][133]

Vaccine production techniques are evolving. Cultured mammalian cells are expected to become increasingly important, compared to conventional options such as chicken eggs, due to greater productivity and low incidence of problems with contamination. Recombination technology that produces genetically detoxified vaccines is expected to grow in popularity for the production of bacterial vaccines that use toxoids. Combination vaccines are expected to reduce the quantities of antigens they contain, and thereby decrease undesirable interactions, by using pathogen-associated molecular patterns.[130]

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One of the most common methods of delivering vaccines into the human body is injection.[13,14,15]

The development of new delivery systems raises the hope of vaccines that are safer and more efficient to deliver and administer. Lines of research include liposomes and ISCOM (immune stimulating complex).[135]

Notable developments in vaccine delivery technologies have included oral vaccines. Early attempts to apply oral vaccines showed varying degrees of promise, beginning early in the 20th century, at a time when the very possibility of an effective oral antibacterial vaccine was controversial.[136] By the 1930s there was increasing interest in the prophylactic value of an oral typhoid fever vaccine for example.[137]

An oral polio vaccine turned out to be effective when vaccinations were administered by volunteer staff without formal training; the results also demonstrated increased ease and efficiency of administering the vaccines. Effective oral vaccines have many advantages; for example, there is no risk of blood contamination. Vaccines intended for oral administration need not be liquid, and as solids, they commonly are more stable and less prone to damage or spoilage by freezing in transport and storage.[138] Such stability reduces the need for a "cold chain": the resources required to keep vaccines within a restricted temperature range from the manufacturing stage to the point of administration, which, in turn, may decrease costs of vaccines.

A microneedle approach, which is still in stages of development, uses "pointed projections fabricated into arrays that can create vaccine delivery pathways through the skin".[139]

An experimental needle-free[140] vaccine delivery system is undergoing animal testing.[141][142] A stamp-size patch similar to an adhesive bandage contains about 20,000 microscopic projections per square cm.[143] This dermal administration potentially increases the effectiveness of vaccination, while requiring less vaccine than injection.[16]

RESULTS

First generation vaccines are whole-organism vaccines – either live and weakened, or killed forms.[168] Live, attenuated vaccines, such as smallpox and polio vaccines, are able to induce killer T-cell (T_C or CTL) responses, helper T-cell (T_H) responses and antibody immunity. However, attenuated forms of a pathogen can convert to a dangerous form and may cause disease in immunocompromised vaccine recipients (such as those with AIDS). While killed vaccines do not have this risk, they cannot generate specific killer T-cell responses and may not work at all for some diseases.[168]

Second generation vaccines were developed to reduce the risks from live vaccines. These are subunit vaccines, consisting of specific protein antigens (such as tetanus or diphtheria toxoid) or recombinant protein components (such as the hepatitis B surface antigen). They can generate T_H and antibody responses, but not killer T cell responses.[citation needed]

RNA vaccines and DNA vaccines are examples of third generation vaccines.[168][169][170] In 2016 a DNA vaccine for the Zika virus began testing at the National Institutes of Health. Separately, Inovio Pharmaceuticals and GeneOne Life Science began tests of a different DNA vaccine against Zika in Miami. Manufacturing the vaccines in volume was unsolved as of 2016.[171] Clinical trials for DNA vaccines to prevent HIV are underway.[172] mRNA vaccines such as BNT162b2 were developed in the year 2020 with the help of Operation Warp Speed and massively deployed to combat the COVID-19 pandemic. In 2021, Katalin Karikó and Drew Weissman received Columbia University's Horwitz Prize for their pioneering research in mRNA vaccine technology.[173]

The idea of vaccine production via transgenic plants was identified as early as 2003. Plants such as tobacco, potato, tomato, and banana can have genes inserted that cause them to produce vaccines usable for humans.[178] In 2005, bananas were developed that produce a human vaccine against hepatitis B[17,18,19]

CONCLUSION

Vaccine hesitancy is a delay in acceptance, or refusal of vaccines despite the availability of vaccine services. The term covers outright refusals to vaccinate, delaying vaccines, accepting vaccines but remaining uncertain about their use, or using certain vaccines but not others. There is an overwhelming scientific consensus that vaccines are generally safe and effective. Vaccine hesitancy often results in disease outbreaks and deaths from vaccine-preventable diseases. The World Health Organization therefore characterized vaccine hesitancy as one of the top ten global health threats in 2019[20]

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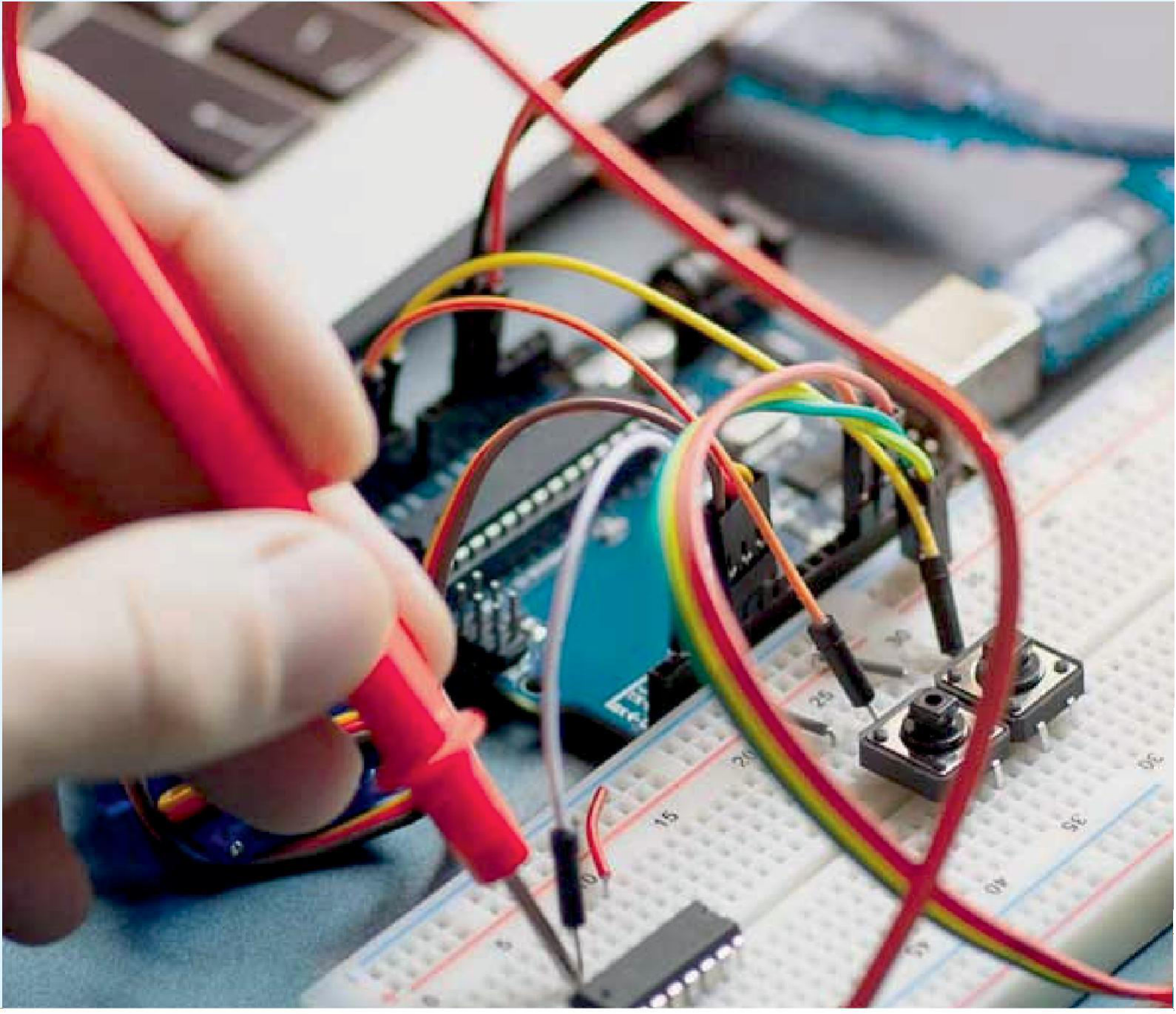

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