EC3067

Emerging vaccine technologies

The potential impact on the cattle industry

Matt Hille, Veterinary Diagnostic Pathologist and Extension Beef Specialist

Are vaccines safe for cattle?

Yes. Animal vaccines are considered "veterinary biologics" and thanks to the Virus-Serum-Toxin Act of 1913, the United States Department of Agriculture's Center for Veterinary Biologics (CVB) exists with the specifically defined task of ensuring veterinary biologics are pure, safe, potent, and effective. These characteristics can be broadly defined as:

Pure: The approved formulation process results in the final product having only products that are intended with no unwanted contaminants.

Safe: Under defined study conditions, there are no adverse effects on the animal or the environment.

Potent: The final formulation has the proper concentration of intended vaccine particles. Not more, not less.

Effective: The product performs as claimed by the approved label claim.

Evaluation of cattle biologics by the CVB requires both pre-licensure and post-licensure testing and monitoring of products. The pre-licensure evaluation provides a rigorous test of the above-mentioned characteristics of a product, while also allowing products to reach market in a timely manner where they can be utilized to prevent disease.

Before a product is licensed, research studies are performed to study the efficacy and safety of the product. When examining the safety of a product, the CVB studies the impact on the intended animal species, unintended animal species (i.e. wildlife, scavengers, other livestock, etc . . .), human health via accidental exposure, and human health via consumption of animal products. If risks are identified, the product is either denied approval or approved with additional required label statements and/or restrictions on the use of the product. An example of the restricted use of a product would be approval in only a specific age or class of animal (such as breeding status or production purpose). Additionally, the CVB itself tests the proposed product in a laboratory environment to assure purity. The facilities responsible for manufacturing the product are also inspected by the CVB.

Post-licensure requirements for approved products require ongoing monitoring of the manufacturing facilities and sale of these products to ensure that the standards originally approved continue to meet CVB expectations. Additionally, much like the vaccine adverse event reporting system (VAERS) used for human products, the CVB collects information on potential adverse events from producers or veterinarians to ensure products that result in unanticipated negative effects are promptly removed from the market.

Are animal vaccines safe for humans in the event of an accidental exposure? Are animal vaccines safe for humans from a food safety perspective?

Yes. No food or health product is without the potential for adverse effects on human health. But, the CVB licensing process ensures that any potential risks to human health are minimized when products are given according to label instructions.

The potential risk to human health from animal vaccines is two-fold. First, because vaccines are administered by humans, the potential for adverse effects of accidental exposure is an important consideration. If vaccines pose a direct risk to humans upon accidental exposure, they are either denied approval or approved under specific conditions. A specific example is the restriction that brucellosis vaccination is to be performed only by a licensed veterinarian.

Second, the potential for residual biologic product to be

present in meat or milk also represents an important consideration. As a part of the licensing process, the CVB examines how long the product is detectable in food animal products and uses this data to determine meat or milk withdrawal periods. The minimum meat withdrawal of all food animal vaccines is 21 days. This means no animal can be legally slaughtered and enter the food chain until 21 days after vaccination. It is important to emphasize this is the minimum withdrawal time for vaccines and any products that remain detectable in animal products beyond 21 days are given appropriate longer withdrawal periods as stated on their respective label.

Overall, the rigorous licensure process overseen by the CVB ensures that any potential risk to human health via accidental exposure to food animal biologics is minimal, and that food animal products are completely free of any detectable biologic products when they reach the consumer.

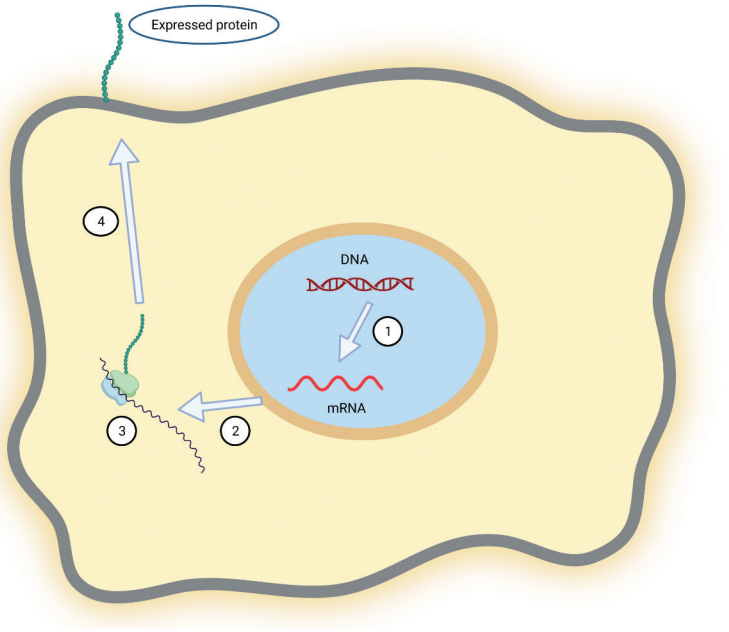

Fig. 1: The normal flow of information for protein production in the mammalian cell. DNA is transcribed into a single strand of messenger RNA (Step 1) that is exported from the nucleus (Step 2). The mRNA transcript is translated into protein by ribosomes (Step 3), which are transported to the cell surface to be expressed (Step 4).

Are there different types of vaccines?

Traditionally, most manufacturers have utilized whole-cell formulations when developing vaccines for animals. This means the entire pathogen (either virus or bacteria) is administered to the animal in order to mimic infection and promote an effective immune response aimed specifically at that pathogen. This results in a "primed" immune system capable of recognizing and eliminating the pathogen in the future should that animal encounter the specific pathogen.

These vaccines can be broken down further into two groups: 1) inactivated and 2) modified live.

An inactivated whole-cell vaccine is simply an intact virus or bacteria that has been inactivated (i.e. killed) to inhibit the pathogen from proliferating in the animal, but still allow for exposure of pieces of the pathogen to the immune system. Modified live vaccines are manipulated to decrease the ability of the pathogen to cause disease but allow for low-level replication in the animal to mimic a real infection and again promote recognition by the immune system. For example, if a specific viral protein is known to be crucial to cause disease, we can develop a modified live version of that virus to use in a vaccine that removes the crucial protein. The result is a virus that is either incapable or very limited in its ability to cause disease relative to the wild type form, but still replicates and produces other viral proteins that the immune system can recognize as specific for that pathogen.

As a general rule, a modified live viral vaccine is going to more closely mimic a natural infection and therefore most often result in a more robust immune response relative to a killed viral vaccine product. If you have vaccinated cattle, chances are you have used each of these vaccine types. Modified live vaccines most often require mixing before administration whereas inactivated products are usually sold ready-to-use.

A third type of vaccine used in cattle are toxoids. Some bacterial pathogens cause disease indirectly by secreting toxins into the surrounding tissue or bloodstream. A toxoid is an inactivated form of toxin that is incapable of causing disease, yet is still able to be noticed by the immune system to promote a robust immune response to the native form of toxin. An example of this type of vaccine used in cattle would be the tetanus toxoid vaccines. Therefore, cattle are not necessarily immune to the bacteria that causes tetanus, but their immune systems are capable of recognizing, binding and disabling the disease-causing toxin that the bacteria secrete.

As our understanding of immunology and vaccinology has progressed over time, this knowledge has been leveraged to create other types of promising vaccines as well. Some examples would include subunit vaccines that focus an immune response to only a defined part of a pathogen as well as vaccines made of nucleic acid (either DNA or RNA). At the time of this writing, only inactivated, modified live, and toxoid formulations have full approval for use in cattle.

Recently, RNA vaccines have received attention from popular media, which has raised concerns from consumers regarding the animal and human health associated with

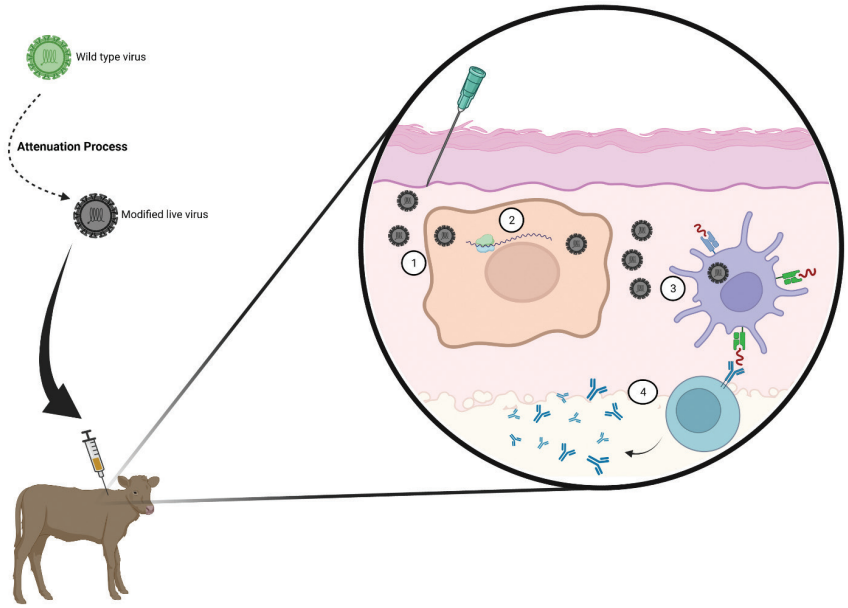

Fig. 2: How traditional modified live vaccines work using bovine viral diarrhea virus as an example. The wild type virus is attenuated (weakened) to allow replication, but minimize the ability to cause disease. Once injected, the modified live virus enters and infects a host cell (Step 1). Within the host cell, ribosomes make proteins from viral RNA to result in viral replication (Step 2). The newly synthesized viruses are secreted from the host cell and internalized by immune cells (Step 3). Within the immune cell, the virus is broken down into protein fragments to be displayed on its cell surface. Lymphocytes (in this case a B lymphocyte) are able to recognize the viral proteins being expressed by the immune cell and result in the production and secretion of antibody (Step 4) which will be available for preventing disease should the calf encounter the wild type virus in the future.

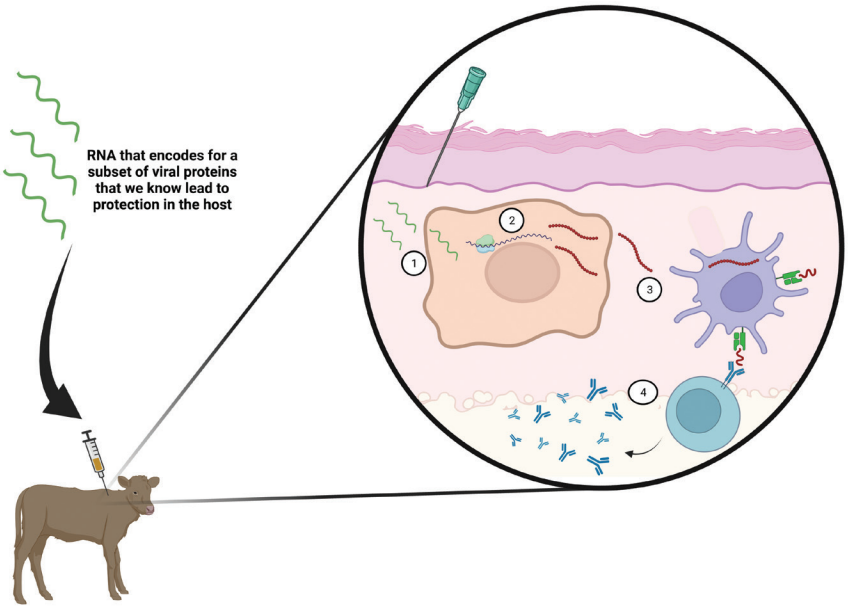

Fig. 3: How RNA platform vaccines work. RNA that specifically encodes for viral proteins that we know offer protection from disease are included in the vaccine formulation. The RNA within the vaccine is take up by a host cell (Step 1). Ribosomes within the host cell produce the proteins of interest (Step 2). These proteins are noticed by immune cells which uptake the proteins and process them to smaller fragments to be expressed on their cell surface (Step 3). The viral protein fragments of interest are recognized by lymphocytes (in this case a B lymphocyte), which induces secretion of antibody that is specific for that specific protein fragment (Step 4). The antibodies are then available to prevent disease if the calf were to encounter the wild type virus in the future.

this particular vaccine format. As mentioned above, there are currently no RNA vaccines approved for use in cattle. That being said, there are numerous benefits to this type of vaccine format that have been observed in other animals and humans and it is likely the same benefits can be used to promote cattle health. Any future RNA vaccine formulation approved for use in cattle will only do so after satisfying the above-mentioned licensure requirements set forth by the CVB.

RNA vaccines offer several advantages compared to traditional modified live or inactivated formulations. To best understand how RNA vaccines work, it is crucial to understand that in biology the flow of information at the cellular level involves DNA sequences that encode and produce specific RNA sequences, which are then processed into proteins. As mentioned above, the benefit of modified live products over inactivated is that the modified live vaccine will induce RNA production that results in proteins that can be recognized by the immune system. For inactivated products, there is no protein production and the only protein available to be recognized by the body is that which is included in the initial dose.

RNA vaccines also induce protein production like modified live vaccines, but do so with fewer moving parts making a cleaner and more efficient process of protein production. The RNA sequences used in vaccines are chosen to represent only proteins known to be protective to the host receiving the vaccine. Therefore, the majority of virus and viral proteins are removed from consideration making any chance to cause wild-type disease effectively zero. Overall, this technology results in a vaccine that is at least as effective as a modified live product, but with substantially fewer components, which, in turn, generally decreases the risk of adverse effects to the host. As mentioned, RNA is produced by all of our traditional modified live vaccines (in animal or human health) so the concept of introducing bacterial or viral RNA to the host is nothing new. RNA is not capable of manipulating or integrating into host DNA. The RNA does not have access to the nucleus where DNA is housed and additionally, they are completely difference nucleic acids. That is, even if RNA could penetrate the nucleus of

a host cell (which it cannot), they "speak different languages", making any manipulation or integration of host cell DNA physically impossible.

To reiterate, there are currently no RNA vaccines on the market for cattle. But the potential of this vaccine platform has proven to be very safe and efficacious in other species so it is likely we will see RNA vaccines in the cattle industry in the future. Currently, the costs of production and researching which proteins are the most important are fairly high but as with all new technologies the cost will likely come down as these processes are made more efficient over time. When they do become available for use in cattle, they will represent a more efficient disease-prevention process than traditional vaccines with fewer particles in the vaccine capable of causing adverse effects to either the animal receiving the vaccine or humans consuming animal products.

Take Home Points:

The licensure process for veterinary biologics is specifically designed to approve vaccine products that are pure, safe, potent, and effective.

The licensure process attempts to balance stringent requirements capable of detecting adverse effects, while at the same time allowing products to reach the market in a timely manner. In the unlikely event a product displays unforeseen adverse effects after reaching the market, continually recording adverse events allows the CVB to remove any product from the market in a timely manner.

All living cells produce RNA. In order to work effectively, traditional vaccines rely on RNA production that encode for the production of viral proteins by the host cell.

RNA vaccine technology is a way to tailor a vaccine to produce only the proteins of interest, without the risk of using the whole virus or bacteria, making the likelihood of unwanted effects or illness lower than traditional formulations. This is particularly true when comparing RNA vaccines to modified live vaccines which can cause mild forms of disease.

RNA does not modify or integrate into host cell DNA.

In humans and other animal species, RNA vaccine technology has shown significant improvements in safety and efficacy compared to traditional vaccine platforms.

If/when RNA vaccines reach the cattle industry, vaccine withdrawal times will be appropriately assigned to ensure no residual vaccine RNA is present in animal products just as they have been used in the past for cattle vaccines. The result will be a food supply that is as safe as it has ever been.

Regardless of the vaccine type used in cattle, proper handling and administration should be followed as directed by the approved label.

For more information on the licensure process for veterinary biologics please visit:
https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_about_vb

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