Prescription platform and autogenous vaccines – what are they and what is the difference?

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Abstract

Autogenous vaccines – farm- and ranch-specific – have been used for decades to prevent and control diseases where commercial vaccines have not been effective. Since the 1970s, the United States Department of Agriculture's Center for Veterinary Biologics (CVB) has regulated the production of autogenous vaccines that are produced for interstate and intrastate use. In 2018, CVB extended this "autogenous" production to platform technology which allows an opportunity for a wider number of agents to have "prescription" vaccines developed. These "prescription" platform (RxP) vaccines can express the important immunizing antigens rather than the whole organism in traditional inactivated autogenous vaccines There is a difference in the specificity and safety of autogenous and RxP vaccines, but both need to be administered with an adjuvant. They each have their advantages and disadvantages. These vaccines are tested for safety and purity, but there is no guarantee of efficacy.

Key words: vaccines, autogenous, prescription

Introduction

In 2018, the United States Department of Agriculture (USDA) Center for Veterinary Biologics (CVB) published a Memorandum on the Prescription Platform Vaccines.[1] This provided an additional mechanism for producers and their veterinarians to develop vaccines quickly for use in preventive programs. Like autogenous vaccines which have been available for as long as there have been vaccines, these vaccines are directed for use on specific farms and herds where there are no currently licensed vaccines and/or where current vaccines are not efficacious. Like autogenous vaccines, these vaccines must be tested for safe and purity, but there is no claim of efficacy. In this paper, I will discuss the similarities and differences between prescription and autogenous vaccines.

Autogenous vaccines

Autogenous vaccines are one of the tools of bovine preventive health programs and have been extensively used for 50 years. They fill a void when new agents emerge for which there are no vaccines or when antigenic variation occurs that is outside the spectrum of protection afforded by commercially available vaccines.[2] They have value in filling these gaps or in cases when diagnostic and molecular workups of isolates have shown the need for different antigen. However, at other times autogenous vaccines have been touted as a panacea or "miracle cure" and the answer to all problems without any efficacy data and are often based on antecdotal "evidence". They are regulated by CVB, and they require a Veterinarian-Client-Patient Relationship (VCPR).[3] In cattle, autogenous vaccines have been most widely used to prevent bacterial infections with *Mycoplasma bovis, Mannheimia haemolytica* and *Moraxella bovis* along with the plethora of other "pinkeye organisms". They have also been used for bovine mastitis organisms. Viral autogenous vaccines have been more limited, but have included members of the bovine herpesvirus family including bovine herpesvirus 1 (infectious bovine rhinotracheitis virus) bovine herpesvirus 2 (bovine mammilitis virus) and bovine herpesvirus 4 (gamma herpesvirus associated with reproductive and respiratory disease) along with many other viruses identified with a herd problem. The organism (virus, bacteria, etc.) from the premise is isolated and then grown. For most bacteria, the isolation and growth in media is straightforward. Viruses, on the other hand can be much more difficult to isolate and to grow to produce a vaccine. Most autogenous vaccines use the whole "organism" (Figure 1), and all autogenous vaccines are inactivated. The autogenous vaccines also contain an adjuvant to enhance the immune response. The inactivated vaccines are then tested for safety and purity. There is no guarantee of efficacy.

Prescription platform vaccines

In 2018, the CVB approved licensing guidelines for production platform technology-based, non-replicating, nonviable vaccines.[4] Using this guideline allowed veterinary vaccine manufactures to fully license a vaccine and optimize all manufacturing processes including the cell lines and vectors (Figure 2). This must be produced in a CVB-licensed vaccine production facility. Once the "platform" is licensed, the platform can be used for prescription platform (RxP) vaccines.[1] Like autogenous vaccines, they require a VCPR and are site-specific. The advantage that RxP vaccine technology has is that any gene of interest (GOI) from a pathogen can be expressed in the vector system and produced using the "licensed" platform. Veterinary RxP vaccines fall into 2 general types, RNA particle (Figure 3) or expressed protein (Figure 4). A third platform, mRNA, have not been commercialized in cattle. The RNA particle is a non-infectious "virus" that carries the mRNA into the cell where the mRNA is amplified, and proteins expressed. There are no "pure" mRNA vaccines like the COVID 19 mRNA vaccines in livestock yet. The "pure" mRNA vaccines do not amplify the mRNA. The second type, "the expressed protein" (Figure 4) occurs when the vector containing the GOI is used to infect cells in vitro and the protein is expressed in vitro. The protein is then harvested, and the protein is then the antigen. Just like autogenous vaccines, an adjuvant is added to enhance the immune response. The RxP vaccines are then tested for safety and purity. Like autogenous vaccines, there is no guarantee of efficacy.

Comparing autogenous to RxP

In general, the RxP vaccines are more effective at expressing viral antigens because all that is needed is the target gene (protein) and not the whole virus (Figure 1, Table 1) . Because many viruses are difficult to isolate and grow, the use of molecular techniques can be used for detection and generating the viral sequence. Having the virus sequence allows the target gene to

Figure 1: Autogenous whole pathogen vs. subunit prescription vaccines. The "whole" pathogen contains all the antigens while the subunit prescription vaccines contain the important immunogens.

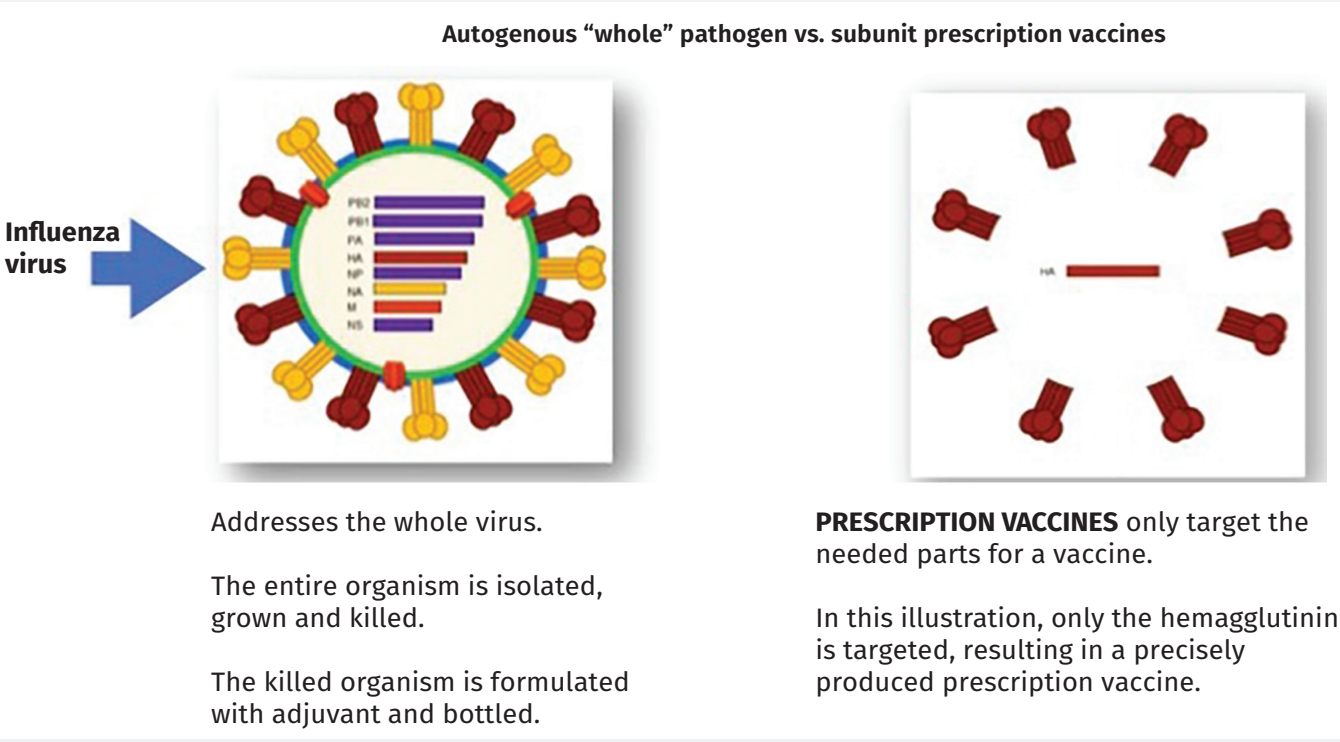

Figure 2: Overview of the USDA Licensed Platform Vaccines. The process involves developing a "licensed" vaccine that results in a "production platform license" (green box 1). The licensed platform is used to produce a commercial vaccine with proven potency, efficacy, safety and purity (green box 2). This licensed platform can then be used as a platform for prescription platform (blue box 3) and target genes can be swapped out on a "specific" farm or ranch to produce prescription platform vaccine (blue box 4).

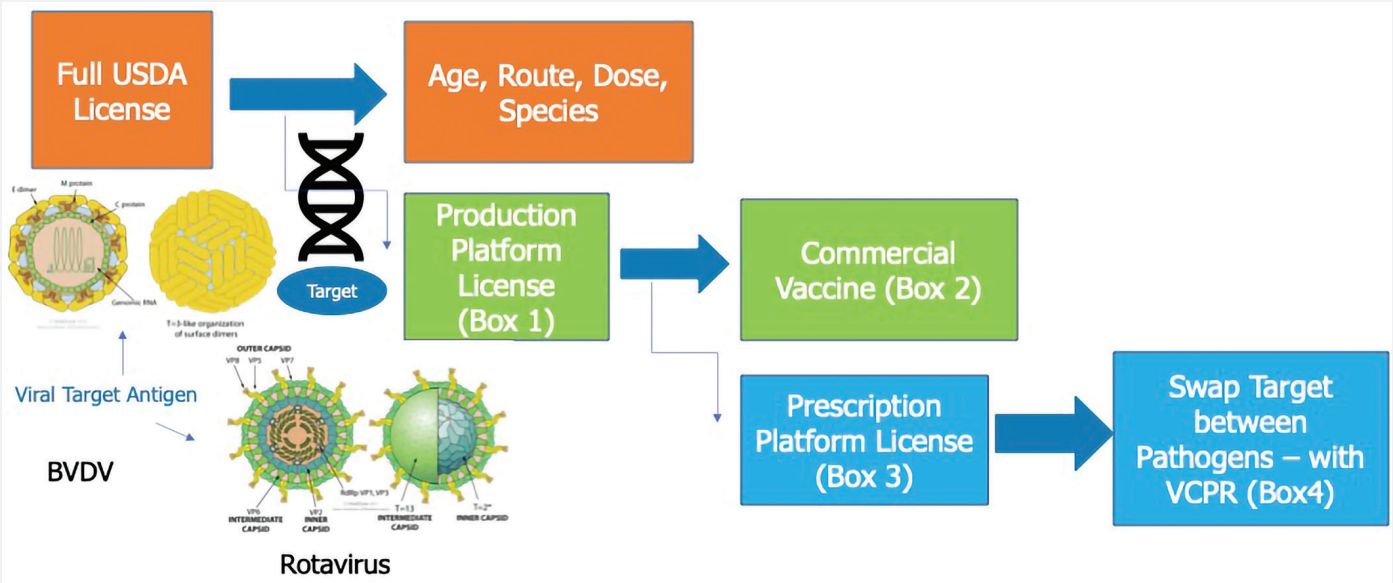

Figure 3: Platform Vaccines-RNA Particle. One type of currently marketed RxP animal vaccines uses RNA particle which is different from a "pure" mRNA vaccine like those seen with COVID19. The RNA particle is administered with an adjuvant. These RNA particles infect the animal's cells producing more mRNA that is than translated into proteins. These RNA particles cannot produce infectious virus.

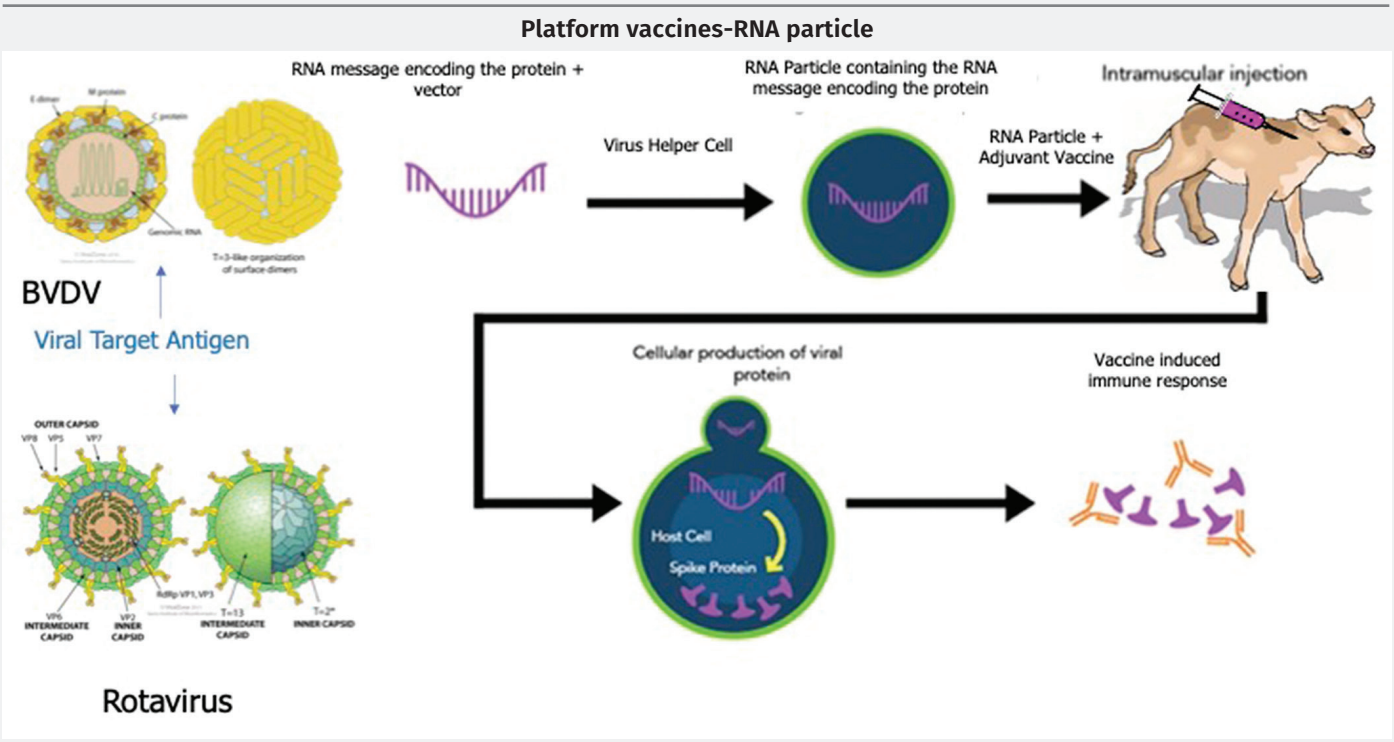

Figure 4: Platform Vaccines-Expressed Proteins. One type of currently marketed RxP animal vaccines uses expressed proteins. These expressed proteins are produced in in vitro cell culture and the protein is purified and protein is formulated with an adjuvant. This vaccine is administered to the animal like an inactivated vaccine.

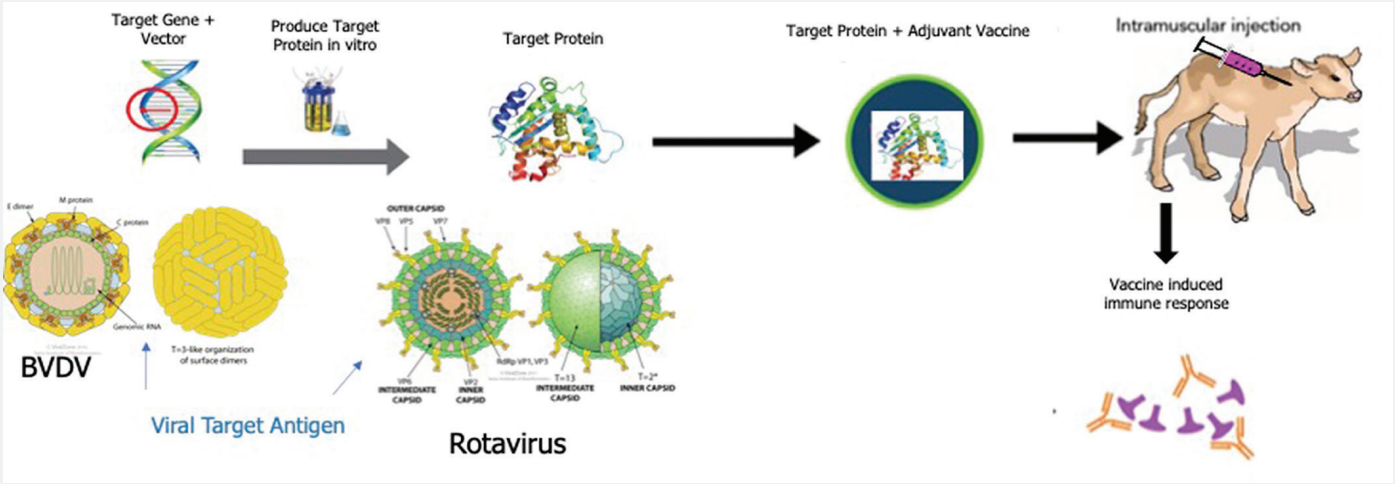

Table 1: Comparison of Autogenous vs. RxP Vaccines

Autogenous	RxP
Derived from an isolate -- low success rate for viruses that are hard to grow.	Derived from a Gene of Interest (GOI) Sequence.
The entire organism is isolated from the originating farm and killed.	High success rate for viruses that are hard to grow.
The killed organism is formulated with adjuvant.	The subunit, targeted proteins are formulated with adjuvant.
Adjacent/non-adjacent documents and VCPR needed to use on other farms.	Conveniently available through a Veterinarian-Client-Patient Relationship (VCPR).
Reactive target, whole virus or bacteria.	Recent target, GOI sequence only.
Master seed isolates expire.	Short development cycles.
Efficacy unproven.	Safety proven, efficacy unproven (initial product is fully licensed with proven efficacy).

be synthesized and expressed in the platform and the vaccine can be made. Since the platform has already been "approved" the development and production time can be just a few weeks. Also, because the platform has been fully "licensed", safety has already been established with the licensed "antigen". RxP also have the advantage that multiple antigens can be expressed using the platform and combined. On the other hand, since most RxP platforms are based on eukaryote-based virus and cells platforms, the antigens have "eukaryotic" protein processing making them less effective than autogenous for bacterial antigens since prokaryotes use a different "prokaryotic" protein processing. This has made the whole cell autogenous vaccines more effective with bacterial antigens. The downside of the whole cell bacterial vaccines, antigens is the presence particularly in Gram negative vaccines of lipopolysaccharide (LPS- endotoxin). LPS results in general activation of the immune system that can interfere with a "proper" immune response. The presence of LPS and other whole cell antigen affects the safety of the vaccine. Platforms based on prokaryote systems are being developed.

Summary

Autogenous vaccines have been an adjunct to veterinary practice for over 50 years. Prescription platform vaccines represent a novel approach to providing vaccines for agents that are not easily isolated and provide a more targeted approach that can allow the use of antigens from multiple pathogens. Most of these vaccines have been developed for viral pathogens. Since prescription platform vaccines are based on a licensed vaccine manufacturing process, their production is often on a shorter turnaround time. These vaccines are then tested for safety and purity and there is no guarantee of efficacy.

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