OPEN LETTER

Animal derived antibodies should be considered alongside convalescent human plasma to deliver treatments for COVID-19 [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract
Published data on the first 5,000 coronavirus patients to receive plasma shows promise in the United States. However, delivering convalescent plasma therapies in low- and even middle-income countries is both difficult and costly. Here we discuss the advantages and disadvantages of antisera raised in animals that may allow poorer countries to control the devastating effects of COVID-19.

Keywords
Covid19, therapy, plasma, hyper-immune sera, antibodies

This article is included in the Coronavirus (COVID-19) collection.
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In a recent editorial published March 27th, Roback and Guarner discuss the possibilities and challenges of using human convalescent plasma to treat Covid-19. Although we wholeheartedly agree with their conclusions, they fail to consider the complementary merits of using larger domesticated animals to generate similar clinical benefits, that avoid the considerable regulatory and logistical hurdles arising from the use of human donors.

While showing recent clinical promise and near immediate availability, human convalescent plasma is expensive and time consuming to process due to the need to screen for human pathogens and requires the identification of donors with high neutralising anti-SARS-CoV-2 titres. At the time of writing a routine diagnostic to detect hyper-immune individuals is still not routinely available, while generating large amounts of product to satiate current clinical demand may not even be possible, as manufacturers with the skills to make enriched antisera to scale will still need capacity to generate other plasma therapies for equally pressing diseases, e.g. IVIg for the routine treatment of neurological disease.

In lower middle- and low-income countries (LMICs and LICs), plasma products are expensive and often scarce, due to lack of import from higher-income countries, insufficient local supply of plasma, and lack of infrastructure to establish plasma manufacturing capacity. These factors contribute to the poor availability of human convalescent plasma in LMICs and LICs where deaths from COVID-19 are likely to be very substantial indeed. While human convalescent sera may not be readily available in outbreak situations, antisera of animal origin containing high titres of neutralising antibody can be produced in 2-4 months. Animal-origin purified IgG and IgG fragment preparations are still routinely used as antivenoms, and even though immunization of horses with inactivated Ebola virus (EBOV) failed to yield effective therapeutic antisera, equine hyperimmune sera produced using EBOV virus-like particles conferred protection against lethal challenge in rodents. That antisera generated in horses can potently neutralise SARS-CoV-2 in vitro has also recently been observed.

Until a reliable vaccine or therapeutic intervention becomes available, for LMICs and LICs, we therefore advocate immunisation of larger animals, e.g. horses and sheep, such as is already the standard to generate antivenoms, anti-toxins, and anti-rabies therapeutics for human use. The polyclonal nature of antisera raised in animals makes it particularly suited to neutralising multiple antigens, toxins and enzymes that in humans bitten by snakes cause coagulopathies that are also observed in COVID-19 patients. The animal approach is still used today in the treatment of diphtheria, a potentially fatal respiratory disease caused by a toxin-producing bacterium Corynebacterium diphtheriae. The method, which harvests antibody-rich serum after injecting the diphtheria toxin into horses may appear antiquated, but it nonetheless saves lives.

Furthermore, as equine and ovine hyper-immune sera are already licensed therapies routinely used throughout the world, including Europe and North America, we suggest there would be less of a requirement for time-consuming phase 1 safety testing, as there is already a reasonable, although clearly not perfect, safety profile for animal derived immune sera administered through the i.v. route to critically sick patients. A recent publication that domesticated cats are highly susceptible to SARS-CoV-2 may also favour approaches to develop antisera for their protection and treatment.

Although animal derived immunoglobulins provide effective treatments for the aforementioned indications, consideration must be given to the safety of such therapeutics. Intravenous administration of animal derived immunoglobulins is associated with the development of early and delayed (5 – 14 days post administration) adverse reactions, known as serum sickness. The incidence of adverse reactions to animal immunoglobulins shows great variation between products (from 3% to 88%) and is heavily influenced by quality of manufacturing processes and physicochemical properties of immunoglobulins. Early adverse reactions are often mild (typically, pruritis, urticaria, mild gastrointestinal disturbances), but can on occasion lead to life-threatening anaphylaxis. Serum sickness also occurs with intravenously administered human immunoglobulins, and is typically a mild condition that only becomes clinically life-threatening when doses of immunoglobulins are administered on multiple occasions, at high dosages, or over prolonged periods of time. During a one-off infusion, early adverse reactions and subsequent serum sickness can be carefully monitored and pharmacologically controlled. Nevertheless, these routinely manageable early and delayed reactions may be a risk worth taking over the alternative currently unmanageable and, unfortunately, frequently fatal severe SARS-CoV-2 infection.

The recent excitement and potential usefulness of convalescent hyper-immune IgG must however be tempered by observations that anti-SARS-CoV-1 antibodies can contribute to severe acute lung injury. This has been shown to occur through productive engagement of FcγRs expressed by alveolar macrophages that induce cytokine storms leading to Acute Respiratory Distress Syndrome (ARDS). Animal derived IgG most likely do not optimally engage functional in vivo responses from human FcγRs and may yet turn out to be superior to human convalescent IgG for the short-term treatment of patients with ARDS.

Mitigation of adverse reactions can also be controlled during product development. For example, enzymatic cleavage of neutralising IgG into F(ab′)2, or removal of N-linked glycans from the Fc, are tried and tested approaches to limit interactions with human immune receptors that may give rise to the observed adverse events associated with injected antibodies. Other options currently being investigated include using cattle transgenic for human immunoglobulin genes and glycosylation humanised pigs, but scaling-up manufacture from the limited animals available (difficult to breed) from single for profit companies.
would appear insurmountable in the short term to satisfy escalating demand in LICs and LMICs.

Although the use of animals in medicine has fallen out of favour with the general public, the scale of the current crisis requires a multi-pronged approach that will inevitably involve the holistic and complementary use of animals to control SARS-CoV-2 and future emerging viruses that affect both humans and the animals they live with.

Data availability
No data is associated with this article.

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Open Peer Review

Current Peer Review Status:  

Reviewed by: Fernando Alberto Goldbaum
Inmunova, Buenos Aires, Argentina

The article correctly points out the usefulness of animal sera for therapeutics of COVID-19. It is a good idea, and well explained but needs some work to improve:

1. The authors should cite other works like this. In this article the authors compare the neutralization power of equine sera derived fragments with convalescent plasma. The authors would find helpful the work of Zylberman et al. to improve this review because in that work a comparison between the in vitro neutralizing capacity of equine derived anti-RBD F(ab’)2 fragments are compared with the average of the neutralizing capacity of convalescent plasma. The authors state there that anti-RBD polyclonal F(ab’)2 fragments have between 50 to 100 times more neutralizing strength than the average human plasma obtained from donors.

2. Fragment F(ab’)2 antibodies should have mechanistic advantages over plasma derived human IgG, this should be emphasized more clearly.

3. This strategy should be useful not only for LMICs and LICs countries, since polyclonal antibodies should have advantages over monoclonal or cocktails of monoclonal antibodies, both during the emergency of pandemics and at the long term. The authors should address a discussion about these advantages.

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Partly
Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Development of passive immunotherapies using protein engineering.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 05 June 2020
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Julien Potet
Medical Department, Médecins Sans Frontières Access Campaign, Paris, France

The article recommends the development of animal hyperimmune globulin serum as a therapeutic option against COVID-19. The publication of this article is very timely, as a lot of attention in scientific journals and media outlets has recently been paid to other types of therapeutic antibody products (e.g. convalescent plasma, human hyperimmune globulin (HIG), monoclonal antibodies), but not much to animal-derived antibodies.

Authors compare the advantages and limitations of animal-derived polyclonal antibody products with human-derived polyclonal antibody products (e.g. convalescent plasma, HIG) but not with monoclonal antibodies. Maybe a follow-up publication should also explore the comparison between animal hyperimmune globulin serum and monoclonal antibodies.

In addition to reviewing the expected clinical benefits and risks of animal-derived products for COVID-19, authors evaluate the scalability and accessibility of animal-derived products, particularly in low and middle income countries. Their statements are presented in a balanced manner. Mechanisms of action are described and supported by key citations.

Occasionally, a few statements would however be stronger if additional citations and clarifications were provided:
  ○ Authors claim that “the incidence of adverse reactions to animal immunoglobulins shows great variation between products (from 3% to 88%)”. Although the statement is true, this
large interval may sound very intriguing for a non-expert reader. A citation would be helpful to know more about the factors for this large variation.

- The fact that manufacturers of human plasma will need additional capacity to produce HIG on top of their traditional product (e.g. IVIg) is correct, but the same argumentation could be used for animal antiserum manufacturers too; the latter will also need to continue manufacturing their marketed products (i.e. antivenom, diphtheria antitoxin, equine rabies Ig) and they will need to find the right balance between production of a new anti-COVID-19 serum and continued production of other antisera.

- Authors claim that “animal derived IgG most likely do not optimally engage functional in vivo responses from human FcγRs”. It would be helpful if authors could share a reference to support that statement. If no reference can be found, it may be helpful if authors could add a couple of sentences to explain why in their expert opinion animal IgG do not optimally engage with FcγRs.

- Authors explain that serum sickness (defined as delayed hypersensitivity reactions) can occur with IVIg. They cite Reference #14. This paper lists different types of adverse reactions associated to multiple IVIg infusions, but I am not sure if any of these reactions can actually be qualified as “serum sickness”. It may be due to my ignorance as a non-expert in immunology, but it wasn't clear to me why this reference was cited to support the claim that serum sickness occurs too in patients receiving IVIg. It would be great if authors could clarify this point.

This is it. Congratulations to the authors for this substantiated open letter!

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Partly

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Antivenom and animal antisera production; monoclonal antibodies for infectious diseases
I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.