DESIGNING A "GOOD LIFE" FOR LIVESTOCK: COULD GENE EDITING IMPROVE FARM ANIMAL WELFARE IN LOW- AND MIDDLE-INCOME COUNTRIES?

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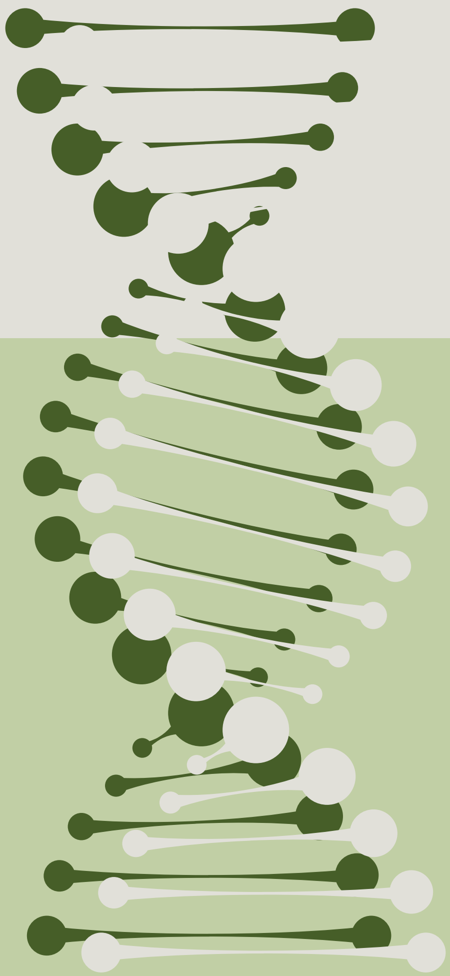

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EXECUTIVE SUMMARY

Although there is no doubt that gene editing represents a powerful technology with considerable potential benefits, the likelihood of its successful application to benefit livestock animal welfare is unlikely in the short to medium term, particularly in low- and middle-income countries (LMICs) given the high costs and low rates of success to date in research settings. Key points covered in this Guidance Memo include the following:

1. **Gene editing currently is biased in terms of certain types of outcomes:** the technology preferentially addresses only those issues that can be targeted by editing, deleting, or replacing a small amount of DNA, and where the results of those changes can be easily measured and assessed. More complex traits associated with animal welfare such as behaviour or condition are less likely to be able to be targeted using gene editing.

2. **Gene editing of livestock has been designed for use in vertically-integrated production systems** [1] and is most likely to be useful within them, as livestock breeding is centralised and breeds themselves are highly standardised which makes targeting traits using gene editing much easier.

3. **There may be specific applications of gene editing that could lead to improvements in animal welfare in certain LMICs**: for instance, using gene editing to bias sex ratios (which is fairly straightforward scientifically) could be particularly valuable in India given the extensive dairy industry, or sex selection in layer hens in Egypt given this is an increasingly vertically integrated production system. Gene editing could also be valuable for producing polled cattle and eliminating the need for mechanical dehorning as currently occurs in many locales.

4. Despite limited regulatory, social, or religious barriers to gene editing, **the widespread development and application of gene editing for animal welfare is unlikely to occur in LMICs in the short- or medium-term** because of the lack of vertically integrated production systems in many LMICs, higher numbers of smallholder farmers in these locales, the likely costs of these technologies, the lack of investment by companies and NGOs on uses of these technologies in LMICs, lack of focus by gene editing researchers on LMICs, and the limited local support for biotechnology research and training in most locales.

5. Where the intensification of livestock production is present and growing, **use of gene editing might be tenable for select traits related to animal welfare but is likely to further accelerate intensification and disadvantage people relying on less intensive production systems**.

6. **Genetic diversity across traditional breeds is valuable and should be maintained**. It is not clear how gene editing could affect this diversity: pushes to more standardised breeds resulting from increased use of gene editing might disadvantage those relying on the use of traditional breeds. However well-adapted indigenous livestock breeds could become an important source for genetic material and identification of important traits with positive welfare implications that could be transferred to more commercialised breeds (which tend to have low genetic diversity) using gene editing and other technologies once these techniques become more refined.

7. **Many of the animal welfare issues in livestock in LMICs are less likely to be addressed through applications of gene editin**g as opposed to lower technological measures such as better access to veterinary services, better management practices, improved biosecurity, and poverty reduction.

[1] Vertically-integrated production systems are those where one company takes over multiple phases of production and distribution to create efficiencies and reduce costs.

CONTENTS

INTRODUCTION

Gene editing techniques have provided humans with abilities to alter the plants and animals on which we depend for food, fibre, and various services. The technology has advanced rapidly in the past decade, allowing breeders to alter specific genetic traits with minimal impact on others (Fahrenkrug et al., 2010). There are countless potential applications for gene editing in animal agriculture, from productivity gains to altering product characteristics (Perisse et al., 2021). However, a key focus has been the potential to improve animal welfare by better adapting livestock to their environment including in response to climate change (Karavolias et al., 2021).

Population growth, urbanisation, and increased incomes, have increased the global demand for animal products, with much of this demand coming from low- and middle-income countries (hereafter LMICs), prompting investment and intensification in their domestic livestock sectors (Parlasca & Qaim, 2022; von Keyserlingk & Hötzel, 2015). LMICs are now some of the largest producers of animal food products, including milk, eggs, and cattle, substantially contributing to national economies and household incomes (Herrero et al., 2013). However the importance of animal welfare both as an inherent value and a means of sustaining production and improving public health is not widely recognised in some of these locales (Parlasca et al., 2023; Qekwana et al., 2019). Animal welfare regulation and access to veterinary care are patchy in many LMICs (Qekwana et al., 2019). It is therefore reasonable to ask whether animal welfare could be improved by adapting livestock to these production environments including through use of gene editing.

In the development of this Guidance Memo, we set out to explore whether gene editing could improve farm animal welfare in LMICs. Despite numerous relevant applications of gene editing currently being explored in research settings, and limited regulatory, cultural, or religious impediments to its use in LMICs, we found that the prevalence of less vertically-integrated, industrialised systems and non-standardised species in these countries, together with likely high cost, lack of investment in gene editing in LMICs by biotech companies and NGOs, and lack of local biotech resources, makes its use unlikely in the short- to medium-term in LMIC livestock production systems particularly for traits associated with animal welfare.

In this Guidance Memo, we outline the potential uses of gene editing in livestock production for animal welfare purposes. Based on in-depth literature analysis of scholarly articles, policy documents, and grey literature, we explore how proposed uses of gene editing in livestock align (or fail to align) with animal welfare priorities in LMICs. Based on these considerations, we provide a summary of where gene editing might have potential for benefit in terms of livestock animal welfare in LMICs and raise a series of cautionary notes about the likelihood of its widespread deployment in these locales at least in the short- and medium-run.

Livestock are domesticated terrestrial animals that are raised to provide a diverse array of goods and services such as traction, meat, milk, eggs, hides, fibres and feathers.

- FAO 2023b

WHAT IS GENE EDITING?

Gene editing is an umbrella term which includes the use of several tools to change the genetic 'blueprint' of plant, animal, or human cells. This genetic blueprint is made up of DNA, which contains the information that cells use to build and maintain living organisms. Together with our cultural and natural environments, DNA determines much about the traits that living organisms develop.

Gene editing uses molecular tools (such as CRISPR cas9) to cut a cell's DNA at a particular location and to add, delete, or substitute a piece of DNA (see Figure 1). When the cell repairs the cut strands, it can disrupt the function of the gene, causing what is known as a 'knockout' or loss of function. However, the molecular tools can also be equipped with replacement strands of DNA (also known as donor DNA), which can provide a template for the repair, described as a 'knock in,' and can be achieved using DNA from the same (called 'cisgenic') or a different species (termed 'transgenic') (Gaj et al., 2013; Mueller & Van Eenennaam, 2022).

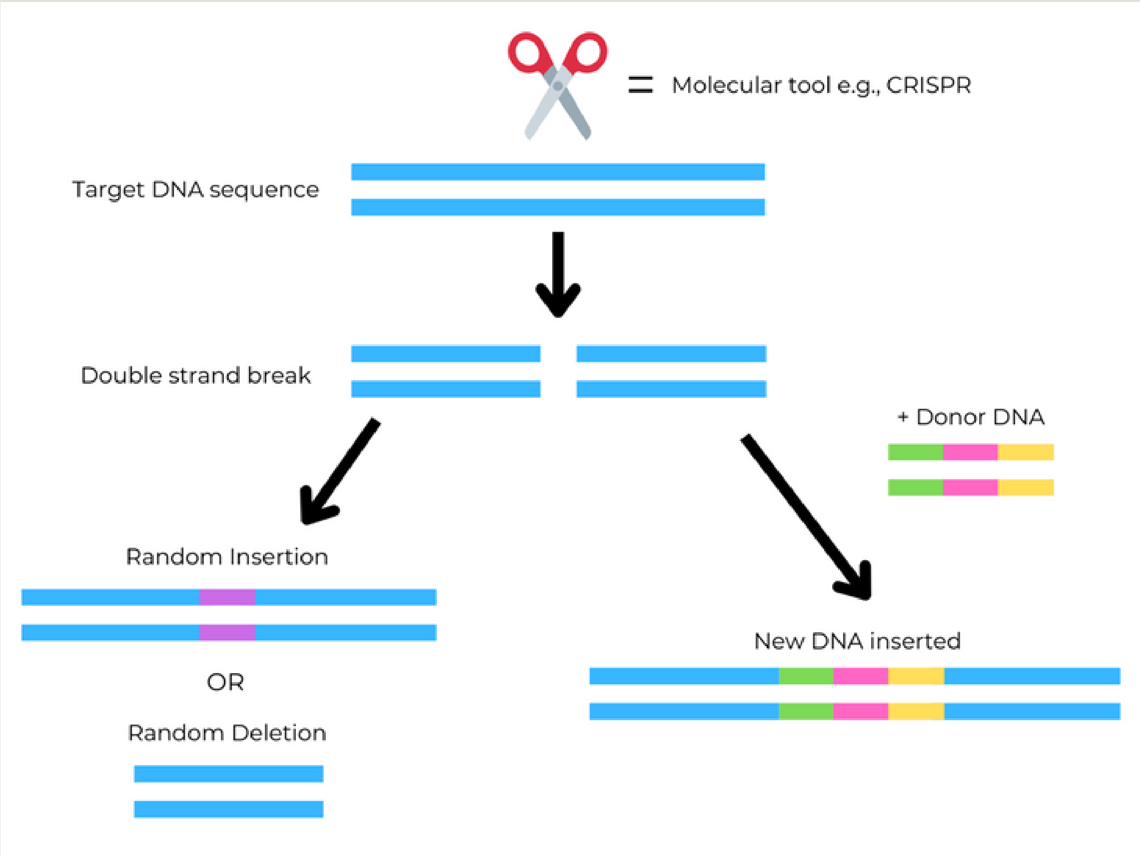

Figure 1: Illustration on the process of gene editing using a molecular tool (e.g., CRISPR), where a random insertion (or deletion) occurs, or donor DNA is inserted

How is gene editing different from other forms of manmade genetic changes?

In some ways, gene editing can be viewed as a continuation of earlier low-tech interventions used in agriculture, including selective breeding,[2] genetic selection,[3] and genetic engineering,[4] typically combined with artificial reproductive technologies[5](Mueller & Van Eenennaam, 2022). As with earlier methods, gene editing facilitates the improvement of desired traits, such as those described in section 4.3 below. In addition, gene editing overcomes some of the limitations of earlier methods (see detail below). Thus compared with gene editing, earlier methods of altering livestock genes are relatively blunt and often inaccurate tools.

Advantages of using gene editing over other breeding methods

The molecular tools used in gene editing in principle work in any species of plant or animal (Shriver & McConnachie, 2018).

Gene editing is relatively easy and cheap to perform: the most recently developed gene editing tool, CRISPR, is often described as a 'democratising technology' because it makes genetic improvements accessible to a wider range of breeders (Abis & Hollemaert, 2018), but it is less clear whether that will be the case in LMICs.

Gene editing can introduce new alleles (versions of genes) that do not already exist in a population or species, thus producing traits that cannot be achieved through selective breeding (Fahrenkrug et al., 2010).

Gene editing can introduce new traits with minimal impacts on non-target sections of DNA that determine other traits (NASEM, 2017).

Gene editing uses programmable guide molecules to target and alter specific genes without affecting other parts of the genetic blueprint (Carlson et al., 2014; Fahrenkrug et al., 2010).

Gene editing can alter a heritable trait in a single generation, thereby reducing the time it takes to improve an animal breed (Liu et al., 2022).

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[2] Selective breeding involves selecting parents that have characteristics/traits of interest in the hope that their offspring inherit those desirable characteristics/traits.

[3] Genetic selection is a process by which certain traits become more prevalent in a species or population than other traits.

[4] Genetic engineering is the deliberate modification of the characteristics of an organism by manipulating its genetic material.

[5] Artificial reproductive technologies include artificial insemination and embryo transfer.

The biases embedded in gene editing

Although gene editing is a powerful tool that has the potential to revolutionise our abilities to alter livestock traits, it is not a silver bullet, particularly for animal welfare. Gene editing is most useful when used to alter traits that are determined by a small number of genes or in cases where a desired version of a gene is not present within the targeted population and can simply be edited in (Fahrenkrug et al., 2010). However much genetic variation is likely to be determined by less localised interactions between several genes (Fahrenkrug et al., 2010), which suggests that a combination of gene editing and traditional selective breeding might be needed to achieve livestock breeding aims particularly associated with more complex traits such as behaviour.

In short, gene editing is biased in terms of certain types of outcomes: the technology preferentially addresses only those issues that can be targeted by editing, deleting, or replacing a small amount of DNA, and where the results of those changes can be easily measured and assessed. More complex genetic traits associated with animal welfare such as behaviour and condition are much less likely to be able to be targeted using gene editing. Furthermore, many important contributors to animal welfare are not genetic but are largely environmental, and gene editing cannot affect them in any meaningful way. Gene editing is most likely to be used in vertically-integrated production systems where one company owns all of the stages of production. In these cases, livestock breeding is centralised and the breeds themselves tend to be highly standardised, providing clear targets for gene editing efforts due to the high amount of control over the animals and their breeding. Consider poultry farming which often is claimed to be perhaps the most successful example of intensive agricultural production. Although selective breeding has led to dramatic improvements in yield, efficiency, and product quality, other traits have not been as tractable using these techniques, particularly those related to welfare outcomes. Gene editing has been argued to have considerable potential with regard to animal welfare, as it can be used to generate only females in a layer hen operation, eliminating the need to destroy any male chickens that are born. However use in this manner assumes highly controlled breeding systems and commercially standardised breeds, with easy access to laboratories and related resources, which can only be supported in vertically-integrated production systems.

Gene editing is not a silver bullet, particularly for animal welfare,

LIVESTOCK PRODUCTION IN LOW- AND MIDDLE-INCOME COUNTRIES

Livestock are produced at a variety of scales and for a range of purposes in LMICs. Small-scale livestock production for home consumption is still common in many LMICs, as is traditional extensive livestock husbandry serving local or domestic markets (Parlasca & Qaim, 2022). For example, the United Nations Food and Agriculture Organisation (FAO) estimates that 78% of African pork and 51% of poultry are raised in backyard systems (FAO, 2022). However, intensive livestock production with commercial breeds is becoming increasingly common in many LMICs (Parlasca & Qaim, 2022).

Livestock are an important source of nutritional security, labour, and fertilizer that support the livelihoods of rural households in LMICs (Salmon et al., 2020). The FAO estimates that 1.3 billion people worldwide earn their living from livestock (FAO, 2023a). Beyond yielding meat, milk, and fibres, livestock provide transport and traction that enable other forms of production. Historically, the contributions of working animals such as draught horses, ponies, donkeys and mules, camels, cattle, and buffalo are difficult to overstate (OIE, 2022). Livestock are also important assets which store and multiply value for their owners. Governments and aid agencies therefore view livestock ownership as a means to improve quality of life for people living in poverty.

However, the nature of livestock dependence in LMICs is changing. Population growth, urbanisation, rising off-farm incomes, and growing domestic and global demand for animal products provide investment opportunities for livestock producers (von Keyserlingk & Hötzel, 2015). In response to these changes, LMICs are rapidly intensifying and industrialising their livestock sectors (Lam et al., 2016).

Hence we focus here on commercial livestock production serving international and domestic markets, as animals raised by households for their own consumption and other smaller-scale operations are unlikely to directly benefit from any applications of gene editing for animal welfare purposes due both to the technical problems already discussed above in relation to non-vertically integrated systems, and to the potential costs of gene-edited animals.

Structure of commercial livestock production

It is beyond the scope of this Memo to give a comprehensive account of the histories and structures of the diverse livestock production systems in LMICs. The following subsections highlight the most pertinent features and trends in livestock production in LMICs that are important for considering the potential application of gene editing for livestock welfare.

Traditional livestock husbandry in LMICs includes a wide range of livestock species and breeds that are adapted to their local cultural, economic, and environmental circumstances (see Box 2). Consequently, genetic diversity across traditional breeds is high, although isolation and low population numbers contribute to lower diversity within breeds (Scherf & Pilling, 2015). This store of genetic diversity potentially provides sources of adaptive traits that breeders could use to improve the welfare and productivity of other breeds (McManus et al., 2009; Scherf & Pilling, 2015). In contrast, the use of breeding programs and artificial insemination in intensive systems has contributed to the dominance of a small number of highly specialised livestock breeds with relatively low genetic diversity. Increased rates of use of commercial breeds threatens the viability of traditional production systems, including the use of indigenous breeds. Additionally, widespread and unregulated crossbreeding of commercial and indigenous breeds dilutes the distinctive genetic characteristics of indigenous breeds.

The broader context in low- and middle-income countries

Although scientific research might progress to permit opportunities to overcome many welfare issues experienced in livestock production globally, other social, cultural, and political issues also need to be considered including regulation, financial viability, and community and consumer acceptance of the technologies.

It is often said that the science of gene editing is running ahead of regulation. Ideally, decisions about whether and under what conditions gene editing should be permitted require considerable evidence and feedback from relevant experts and broader communities (Gordon et al., 2021). However, many proponents of gene editing are frustrated by the lack of adequate guidelines and regulation with regard to potential future applications (Sprink et al., 2016; Van Eenennaam et al., 2021), including in LMICs.

The broader context in low- and middle-income countries continued...

Gene editing of livestock incorporates a set of novel processes that can contribute to producing a wide range of outputs. As with other forms of agricultural biotechnology, the regulatory frameworks for gene editing tend to focus on either the processes involved (leading to a more general and uniform approach towards gene-edited products) or on the products (resulting in each product being assessed on a case-by-case basis). The former approach tends to be considered more precautionary, and the latter more progressive in terms of the speed of technological advancement (Entine et al., 2021). Support for one or other of these approaches often hinges on the extent to which gene editing is considered to be similar or different to conventional breeding or older GMOs.[6]

An important sticking point in the debate about how to regulate gene editing products has been about which should be designated as transgenic or as genetically modified organisms (GMOs). Supporters of gene editing tend to highlight the substantial technical and scientific differences between gene editing and earlier types of genetic engineering and modification, arguing that gene editing is equivalent to conventional selective breeding (Araki et al., 2014; Sprink et al., 2016), and hence argue that it should not be subject to separate regulation. However these arguments fail to consider that regulation exists in part to allow the public to have trust in processes of oversight, particularly where there are public concerns (Gordon et al., 2021). Thus given that many publics do not distinguish GMOs from products made using gene editing (Entine et al., 2021), it is not so clear that exemption from regulation is appropriate.

The viability of gene editing in LMICs (should appropriate and relevant applications be developed) will in part depend on coordination of gene editing regulations and/or strong biosafety enforcement for transboundary movements of gene-edited animals and their products. Particular international treaties and agreements that are relevant include the Cartagena Protocol on Biosafety (CPB), which was adopted as a supplementary agreement to the Convention on Biological Diversity in 2000 (Secretariat of the Convention on Biological Diversity, 2021) and which governs international movements of GMOs[7] to protect natural diversity and its benefits from the potential negative consequences of modern biotechnology. The CPB establishes a precautionary approach to transboundary movements of GMOs, and includes processes for carrying out risk assessments, information sharing, and notifying relevant countries about any transboundary movements of GMOs (Secretariat of the Convention on Biological Diversity, 2000). International food safety standards, risk assessments, and guidelines are developed by the Codex Alimentarius Commission (Sendashonga et al., 2005), and many countries have national authorities and standards regarding food safety, which implicitly or explicitly include genetically modified (GM) or gene edited foods.

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[6] See Table 1 in Friedrichs, S., Ludlow, K., & Kearns, P. (2022). Regulatory and Policy Considerations Around Genome Editing in Agriculture. In Methods in Molecular Biology (Vol. 2495, pp. 327-366): Humana Press Inc. p.329 for an overview of the regulatory approaches for several countries with available gene editing policies.
[7] The CPB uses the term ‘living modified organisms’ (LMOs), which is taken to be synonymous with GMOs.

Similar to what occurred with earlier genetic technologies, gene editing of livestock is likely to result in ongoing intellectual property (IP) claims associated with patenting of genetic changes, processes affected by genetic modification, and even the products themselves, in this case gene-edited animals. Although this is a rapidly changing space, most patents to date for gene-edited animals are held by private companies, most of which are located in HICs (Then, 2016). Hence the traits that are likely to be of primary focus are those that provide efficiency and economic benefits particularly to patent holders, including gene edits that produce more meat (e.g., double muscle trait) and those that might affect behaviours, so-called docility traits (e.g., reduction of production of stress hormones during management and slaughter). These tendencies will combine with the technical biases built into uses of gene editing discussed earlier, which favour less complex traits, and which may well rule out many animal welfare-related traits.

Such patents will be territorially limited, if not subject to access and benefit sharing or trade-related intellectual property agreements (Rukundo & Oliva, 2018). IP claims might place limits on the uses of certain gene editing tools or products. For example, a patent could permit the use of gene-edited animals for milk or meat, but prevent further breeding (Then, 2016), which could raise production costs and further marginalise smaller-scale and traditional livestock producers. Previous biotechnology patents have concentrated the marketing of genetic technology within countries and companies that can more readily afford to pursue patents and protect their IP (Singh et al., 2019; Then, 2016), and similar results are likely with gene editing technologies which in turn would limit their use in LMICs.

Additional economic considerations are bound to strongly affect the development and use of gene editing in LMICs, including for animal welfare. While it is often claimed that lower-cost tools such as CRISPR will make gene editing accessible to developers and users in LMICs or even could 'democratise' these types of technology (Abis & Hollemaert, 2018), the economic outlook remains highly uncertain (Friedrichs et al., 2019). Although gene editing is less expensive to perform than earlier genetic engineering methods, considerable costs still exist (Markets and Markets, 2021), including costs for establishing training, laboratories, and other research facilities and infrastructure necessary to use these technologies, which are largely absent in LMICs, as well as the costs of testing, pursuing regulatory approval, patenting, and promoting and distributing gene-edited products (Brinegar et al., 2017; FAO, 2022; Friedrichs et al., 2022). Uncertainties regarding likelihood and length of regulatory approval and lack of clarity about public perceptions and market adoption increase the risk of investment in gene editing. Thus these barriers to entry may prove insurmountable in the short- and medium-term for small and medium enterprises and LMIC-associated governments that might wish to establish their own gene editing programs. They also should be considered by any NGOs who might wish to establish programs in LMICs, as some of these issues will remain problematic for any ongoing use of gene editing for livestock even if initial investment is provided.

CASE STUDY - India and government investment in biotech

India was proactive in pursuing agricultural production improvements through biotechnology. Already in 1986, the Department of Biotechnology (DBT) was established under the prevue of the Ministry of Science and Technology (Ghose & Bisaria, 2000). A concerted effort by the Indian government, along with international partners, has contributed to the growth of the biotechnology sector including world class biotechnology research and education centres (Ghose & Bisaria, 2000). Considerable advances in livestock improvement (including vaccine developments) had been achieved using earlier forms of genetic engineering at Indian research institutes prior to the development of novel GEd tools (Ghose & Bisaria, 2000). India is therefore well positioned to develop and adapt gene editing methods to target the needs of local livestock producers.

The release of CRISPR has spurred a rapid increase in public and private investment in gene editing for human health, agriculture, and industrial applications (Brinegar et al., 2017). Often the public sector funds initial exploratory research in emerging fields, while private investment is used to develop marketable products (FAO, 2022). Nevertheless, Whelan et al. (2020, p.3) found that public research and local companies accounted for over half of agricultural new breeding technique (NBT)-related products (of which gene editing is one) reviewed by the Argentinian regulatory authorities to date. Local innovation may be essential for gene editing development, which would represent a deviation from the history of the processes associated with older GMOs. However in contrast to Argentina, most LMICs do not have a robust, local biotechnology industry, with possible exceptions including India which has made significant governmental investment in some of these technologies.

Public perceptions of gene editing will also be important drivers of the likely uptake and use of these technologies. However, little is known about people's attitudes towards the use of gene editing in livestock production[RAA1] (with one exception being Australia – see Ankeny et al. 2021), and even less about the views of people in LMICs. Most studies that have investigated attitudes towards gene editing focus on uses in plants or humans. Additionally, most studies are conducted in middle-income countries (MICs) and HICs, likely because these are expected to be early adopters of gene editing. Studies across a range of MICs and HICs have found greater public acceptance for gene editing than for earlier genetic technologies such as older forms of GM (Gatica-Arias et al., 2019; Vasquez Arreaga, 2020; Yang & Hobbs, 2020). However there are concerns about the potential framing problems inherent in these studies which may exaggerate the support for gene editing (Ankeny and Harms 2021); hence much more research is needed on these points.

As a novel technology, public awareness and knowledge about gene editing is generally lower than for GM (Busch et al., 2022). Calls for increased education are common in studies of public acceptance of gene editing and related biotechnologies (e.g., Kooffreh et al., 2021), as it is often assumed that knowledge about a particular technology will improves its public acceptance. Quaye et al. (2009) call out this misconception and argue that greater attention should be paid to who creates knowledge about biotechnology, and the complex forces that in fact shape people's views about it.

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It has been argued by proponents of gene editing in livestock that people in LMICs will be less concerned than those in HICs about the use of agricultural biotechnologies including gene editing because they face greater threats to food and nutritional security (Mueller & Van Eenennaam, 2022). However, there is no evidence from comparative studies of public views to determine whether this is the case in the limited studies that exist. People in LMICs tend to agree that biotechnology could have benefits for food and nutritional security, as well as other problems in the food and agriculture sectors (Abigaba et al., 2022; Gathaara et al., 2008). Nevertheless, they also raise concerns about these technologies, particularly about potential effects on genetic diversity and the environment, adverse effects on farmers (for instance due to higher costs), and, to a lesser extent, the safety of the technologies and their products (Gathaara et al., 2008).

Other facts such as cultural, economic, and political views are clearly relevant to people's attitudes toward biotechnologies in LMICs. For instance participants in research in the Philippines and Ghana viewed biotechnology as a Western invention that would disrupt their traditional food systems (Aerni, 2002; Quaye et al., 2009). A similar argument argument has been presented by the influential Indian activist and scholar Vandana Shiva, who points to the Green Revolution as an imposition of outside technologies (Ellis-Petersen, 2023). Bandewar et al. (2017) emphasise the mistrust of outsiders and what are viewed as 'dubious NGOs' promising improved incomes or production efficiencies for farmers in Africa. The legacy of past problematic agricultural technology transfers is likely to impact the acceptance and adoption of gene editing particularly in LMICs (see also Wright et al., 2022).

Additionally, people often question who will benefit from agricultural biotechnology. In the Philippines and Mexico, people have challenged the idea that biotechnology might reduce costs for farmers, because they suspect that royalty fees or IP licenses will be required and in fact increase costs (Aerni, 2002). Similarly, expectations that the risks and benefits of the technology would be unevenly shared reduced the acceptability of gene editing for livestock in Southern Brazil (Yunes et al., 2021).

Trust in government also informs people's attitudes towards gene editing and biotechnology more generally. Concern for the potential environmental consequences of agricultural biotechnologies is heightened in places where there are misgivings about governments' abilities to enact appropriate biosecurity measures (Aerni, 2002). There also is evidence that attitudes toward gene editing will differ depending on the potential applications and whether publics view them as important or extraneous (Ankeny et al., 2022; Yunes et al., 2021; Yunes et al., 2019).

There is limited evidence about the effects of religious beliefs on attitudes toward gene editing: many major religions including Islam and many forms of Christianity contend that technologies can be a positive thing if they contribute to improvements in life and health. In most contemporary belief systems, if safety and efficacy issues are resolved, and robust regulations or ethical guidelines are in place to prevent premature or misuse of the technology, many religions think that it is important to prevent harms including to non-human animals, and produce benefit where these benefits are potentially significant. Thus it could be argued that use of gene editing to produce significant improvements in animal welfare is permissible (Kuhmar, D'Souza and Asthana 2018).

...people often question who will benefit from agricultural biotechnology.

Animal welfare in low- and middle-income countries

Animal welfare is a complex and multi-faceted topic: there is no one accepted definition or measure of good animal welfare. Trade-offs between different animal welfare outcomes frequently occur within and across production systems. Such trade-offs occur when the pursuit of one desired outcome limits the ability to achieve another, or is in conflict with a separate desired outcome such as environmental sustainability, human health, or economic growth (Brase et al., 2018). For example, Rault et al. (2022) argue that the freely roaming livestock in many LMICs have greater positive welfare than in industrialised confinement systems, albeit while risking more injuries and greater exposure to infectious diseases.

Legislation regarding animal welfare in LMICs is patchy, with many lacking resources to monitor and enforce existing laws (AU–IBAR, 2017; Doyle et al., 2021; Fraser, 2008; Qekwana et al., 2019). To help address the gaps in legislation and capacity, international and civil society organisations often play important roles by providing animal welfare guidelines, education, and finances (Doyle et al., 2021; Parlasca et al., 2023). The Organisation for Animal Health (OIE) plays a central role in promoting an international framework for appropriate animal health and welfare standards and guidelines (AU–IBAR, 2017; Bayvel & Cross, 2010).

Although it is beyond the scope of this memo to review the diverse animal welfare frameworks in LMICs in any detail,[8] it is important to note that many animal welfare frameworks originated in high-income countries (HICs) in the context of rapid industrialisation of livestock farming (Fraser, 2008). As the production systems that shape the treatment of animals in LMICs are diverse and often distinct from those of HICs (Parlasca et al., 2023), it is important to review what the key animal welfare issues are and consider how gene editing might be able to address them. However we must also note that increased industrialisation of livestock sectors in some LMICs has introduced many of the welfare problems previously associated primarily with HICs.

CASE STUDY - Animal welfare in Egypt

Egypt is recognised as the first country in the Middle East to enact animal welfare regulation (Aidaros, 2005): The Agricultural Law (1966) forbids cruelty to animals as specified by Ministerial Decree. Moreover, the amended Egyptian Constitution (2014 (Art. 45)) guarantees that “The State shall…preserve plant, animal and fish resources and protect those under the threat of extinction or danger, guarantee humane treatment of animals, all according to the law”. Deliberately killing certain animals, including livestock, is penalised under articles 355 and 357 of the Egyptian Penal Code (World Animal Protection, 2020).

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[8] For a review of existing literature of animal welfare concepts in LMICs, see Parlasca, M., Knößlsdorfer, I., Alemayehu, G., & Doyle, R. (2023). How and why animal welfare concerns evolve in developing countries. Animal Frontiers, 13(1), 26-33. https://doi.org/10.1093/af/vfac082

Animal welfare priorities in LMICs and the potential for gene editing

Many key animal welfare issues are largely environmental or human-caused. For instance, many livestock animals have poor physical condition due to the lack of available or affordable resources with which to meet their basic needs (Rault et al., 2022). In many LMICs, appropriate fodder is limited, as is clean and adequate water especially during dry seasons/years. For instance, Kennedy et al. (2018) note that Indian livestock consume indigestible or toxic substances that can cause illness or death due to scavenging for food among discarded rubbish. Consequently, livestock may be chronically malnourished, which affects both physical health and productivity, as well as creating other negative impacts on welfare.

Domesticated working animals used for transport and traction are particularly important in LMICs: despite their importance for income generation, many of these animals suffer poor welfare. Working livestock often suffer from injuries and overwork; poor husbandry practices; mistreatment; inadequate access to feed, water, and shelter; and general neglect (Ali et al., 2016; Ali et al., 2019; Ali et al., 2015; McLean et al., 2019). The OIE attributes the poor welfare of working livestock to insufficient resources, inadequate husbandry knowledge, and dangerous working conditions, all of which are environmental and/or human generated conditions, unlikely to be addressed by gene editing applications.

Lack of adequate shelter is also likely to cause condition issues. Many LMICs have extreme or highly variable climates, including monsoons, tropical humidity, and severe heat. During monsoon seasons, heavy rainfalls combined with inadequate shelter promote hoof disease and infections (Chakrabarti & Kumar, 2016), parasites and other disease vectors (Dappawar et al., 2018; Khajuria et al., 2013; Muraleedharan, 2005; Shakya et al., 2017), and mastitis in cattle and buffalo (Khan et al., 2015; Singh et al., 2021). Condition issues are often exacerbated in commercial and exotic breeds, which have been bred for temperate or highly controlled environments, and high-input production systems (Nielsen & Zhao, 2012).

Although poor overall condition in livestock largely results from environmental and human-caused conditions associated with management, gene editing researchers are exploring certain approaches to some of these issues, such as how to better adapt higher-yielding breeds to lower-quality fodder (Tait-Burkard et al., 2018; Zhao et al., 2019).

As it has been found that indigenous breeds cope better in low-input environments (Mwai et al., 2015), it may be that their genetics could be helpful sources for variation that could allow other breeds to subsist in lower-input environments if these traits were gene edited in, or alternatively these indigenous breeds could be gene edited to allow them to have greater yields.

Similarly gene editing applications might also be applied to help livestock better cope with stressful environments particularly those exacerbated due to climate change. For instance, some gene editing researchers have focused on increasing tolerance to heat in exotic dairy and beef cattle, which are often bred for temperate climates and therefore struggle in tropical or arid regions (Cheruiyot et al., 2022). However it also has been noted that heat stress can be mitigated by use of appropriate which management strategies such as use of shade, sprinklers, and modification of feeding, and that any gene editing for these might well need to be used in conjunction with such management strategies.

Infectious and vector-borne diseases cause high rates of livestock morbidity and mortality, risks to public health from zoonotic diseases, and economic losses to households and industries (Sollner et al., 2021). Infectious diseases and parasites cause suffering and death to thousands, if not millions, of livestock, wildlife, and people in LMICs (OIE, 2023). Although the distribution of diseases varies both within and across LMICs, there are several that are widespread across multiple countries and regions. Disease resistance is not easily achieved through selective breeding as it depends on several linked traits, which has led to an overreliance on antibiotics and the rise of antimicrobial resistance in LMICs (Liu et al., 2022).

However, there are multiple ways in which disease resistance might be achieved through gene editing (Sollner et al., 2021), for instance by protecting livestock from infectious diseases and parasites, or correcting naturally occurring disease-causing mutations which often occur due to inbreeding within small populations, such as might occur in local breeds (Perisse et al., 2021).

Currently preventative measures, including vaccines and biosecurity programs, are the most important methods for managing infectious diseases in livestock, although access to vaccines is limited for small-scale and backyard producers in LMICs (Hopker et al., 2021). Biosecurity measures are also often poorly implemented and enforced not only in backyard farming (Clark et al., 2022; Lohiniva et al., 2013) but also in commercial production (FAO, 2018; Negro-Calduch et al., 2013). Qualified vets and trained veterinary paraprofessionals are essential to improving animal welfare. Not only can they provide diagnostic and veterinary treatments, they ideally are able to monitor the incidence of infectious disease, administer vaccinations, and provide guidance about appropriate husbandry practices and care (Doyle et al., 2021). However, veterinary services are often inaccessible in LMICs (Acharya et al., 2019; Qekwana et al., 2019). It is clear that many improvements in animal welfare associated with disease would be best addressed through better provision of resources and expertise, as well as better management, rather than gene editing.

It is clear that many improvements in animal welfare associated with disease would be best addressed through better provision of resources and expertise, as well as better management, rather than gene editing.

Invasive procedures associated with livestock management can cause stress, pain and suffering that negatively affect livestock welfare. Some of these conditions could potentially be addressed by use of gene editing. These include beak trimming in chickens, dehorning of cattle, nose roping of cattle or pigs, castration and tail docking in pigs and other animals, and mulesing in sheep, many of which are performed without pain relief. Additionally, livestock are often subjected to aggressive handling, violence, and severe stress during such procedures (Asebe et al., 2016), making it desirable to minimise their occurrence.

For instance dehorning is common in intensive dairy production to prevent injuries among densely housed animals or to handlers (Perisse et al., 2021), and often is carried out without anaesthetic, causing pain and stress to calves. Gene editing can be used to introduce a natural genetic variant from Angus cattle into the DNA of dairy cows to produce polled (hornless) animals without sacrificing milk yields (Carlson et al., 2016). This would eliminate the need to dehorn calves. However this approach is unlikely to be valuable in LMICs where many dairy breeds are local and indigenous, with the exception being India where dairy production is increasingly vertically integrated.

Male pigs (boars) are undesirable for pork production because they can produce a strong odour in the meat, known as 'boar taint.' To prevent this, male piglets are surgically castrated within 7 days of birth. In many European countries, castration is no longer permitted without anaesthesia due to concerns about the pain caused to the pigs, but castration is commonly used in most other countries, including LMICs.

As an alternative to castration of male pigs, Friedrichs et al. (2022) used gene editing to determine the sex of offspring and produce only female piglets thus reducing, if not eliminating, the need to castrate pigs in pork production. Other groups have used gene editing to prevent testicular development in male pigs (Sonstegard et al., 2016). Again, this type of gene editing might be useful in production systems that are more vertically integrated but is unlikely to be utilised in most LMICs that produce pork.

Many other procedures that can cause pain and suffering, such as branding, transport in trucks or ships, and eventually culling or slaughter of most livestock that are often cited as important contributors to animal welfare are largely environmental, management, and/or human-created conditions. For instance, animal welfare during slaughter is an important and controversial issue in both many HICs and LMICs. Lack of resources and proper training leads to mishandling during slaughter, which causes pain and stress for animals (Aidaros, 2005). Furthermore, concerns have been raised regarding the welfare of live cattle and other livestock imported to LMICs. For example, live export of livestock from Australia for slaughter in Egypt remains controversial despite upgrades to facilities and improved training and handling by staff (Auty, 2003; Brightling, 2003; Brown, 2003, 2004).

Another domain in which gene editing could contribute to improving animal welfare would be by determining the sex of animals used in beef, dairy, and egg production, which would reduce the number of less productive or surplus animals due to their sex (e.g., male chickens in a layer hen production system, or male cows in a dairy system), which are often culled in intensive systems (Owen et al., 2021). However as discussed above, such usage depends on a highly integrated production system with tight controls over breeding, which is not present in most LMICs at this time.

There is increasing attention in HICs about positive animal welfare relating to the affective states of animals. Such considerations do not appear to be high priorities in LMICs. Where systems are becoming more intensified, livestock are more likely to be confined without access to outdoor areas and denied opportunities to engage in natural behaviours (von Keyserlingk & Hötzel, 2015), conditions which are noted to make negative contributions to animal welfare. Using gene editing to alter animals' affective states[10] would be highly challenging, not least because of the difficulty in measuring affective states in a manner that would allow assessment of the successfulness of gene editing.

A final consideration is that numerous gene editing applications in livestock have been proposed that do not appear to be intended to directly benefit animal welfare. These changes are usually aimed at increasing yields or changing the quality of production outputs: for instance consider applications that increase production efficiencies or yields of meat, milk, eggs, and fibre (Perisse et al., 2021) by disrupting the myostatin gene in cattle, sheep, goats, and pigs to increase muscle growth (Tait-Burkard et al., 2018), or increasing yields of milk (de Almeida Camargo & Pereira, 2022) and wool (Crispo et al., 2015; Li et al., 2017). Other uses of gene editing in livestock are intended to alter product characteristics to make them more appealing to consumers, including elimination of allergens in milk and eggs (Doran et al., 2017; Wei et al., 2018); elimination of boar taint (unpleasant odour in meat) in pork (T. S. Sonstegard et al., 2016); or improved wool quality in sheep and goats (Shao-zheng et al., 2020). However it is important to note that it is unclear whether such changes might result in unanticipated or indirect negative impacts on animal welfare, particularly increases in yields which might place additional burdens on production animals.

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[10] Animals may display quick emotional responses to a stimulus (e.g., a startle response when confronted by a predator), whereas 'affective state' refers to the longer lasting, underlying experience of feeling, emotion, attachment, or mood (such as anxiety or depression) which are not caused by a single stimulus but result from an accumulation of experiences.

In short, many of these gene editing applications are highly speculative, while others do not directly address the key animal welfare issues faced by many in LMICs. Further, some types of modifications produced by gene editing might be viewed negatively by publics including consumers in terms of their contributions to welfare, particularly if the breeds are being modified to be less resource intensive and commercially more efficient, or if there are perceptions that the adaptations could be open to abuse (e.g., increased heat tolerance could cause animals to be more exposed to higher temperatures). However, it must be noted that there are some efforts underway to use precision breeding (gene editing combined with traditional breeding techniques) to make improvements that might be of benefit to dairy animals and smallholder farmers in sub-Saharan Africa: the Bill and Melinda Gates Foundation has recently given a grant to a biotech company to optimise bovine genetics to provide better adaptation to tropical heat, improved milk yield, and better adaptation to local diseases among other traits, along with funding of efforts to support regulatory review and commercialisation activities for these animals in the target countries (Cornall, 2020).

CASE STUDY - Perceptions of biotechnology in Indonesia

Based on a 2002 survey of Indonesian agricultural interest groups (including consumers, scientists, journalists, farmer leaders, policy makers, extension workers, and businessmen), ISAAA reported moderately positive attitude towards agricultural biotechnologies. Survey respondents tended not to believe that biotechnology is hazardous (Torres et al. 2006). but consumers, policy makers, and businessmen believed that GM foods should be labelled. Notably, surveyed businessmen tended not to see much benefit from biotechnology. Most of the interest groups felt that agricultural biotechnology would benefit Indonesian agriculture but were unsure whether those benefits would be shared with Indonesian small farmers.

CONCLUSIONS

As noted throughout this Guidance Memo, gene editing is a powerful technique that could lead to significant changes in certain genetic traits. However, research is in its earliest stages and costs are still high, so that the widespread use of gene editing in highly integrated industrialised livestock production systems in HICs is unlikely in the short- to medium-term, let alone in LMICs which tend to have much less integrated production systems. Even if gene editing were to become more accessible in terms of economics, the technology is biased in terms of certain types of outcomes: it would preferentially address only those animal welfare issues that could be targeted by editing, deleting, or replacing a small number of specific genes, and where the results of those changes could be easily measured and assessed. Hence it is not likely in the short- or medium-term to be effective in cases where traits are complex, such as those that result from the interaction of multiple genes or gene-environment interactions including behaviour. Furthermore, many animal welfare issues that are of most concern in LMICs relate to traits that are largely non-genetic and instead are products of environment including human behaviours particularly associated with livestock management.

Therefore gene editing is likely to be most effectively applied for purposes of improved animal welfare in some very discrete circumstances, such as for sex selection in agriculture where females are preferred (e.g., layer hens and dairy cows) and where systems are highly vertically integrated. More generally, gene editing of livestock is likely to be most useful in vertically integrated production systems where livestock breeding is centralised and breeds themselves are highly standardised. However, gene editing will not replace traditional breeding techniques (such as artificial insemination and standardisation) but is likely to be most effective when used in conjunction with these. Gene editing relies on having a known genome whose functions are well-understood, and these conditions are more likely to apply to standardised breeds that are provided by centralised breeding services as occurs in vertically integrated production systems. In many LMICs, vertically integrated production systems are increasing in number but remain limited, and hence applications of gene editing are likely to be similarly limited in the short- and medium-run.

Where standardised breeding and increasing intensification is present, gene editing is more likely to be useful: some examples in LMICs include the poultry sector in Egypt and the dairy sector in India where sex selection might be especially valuable. But it must be noted that these and other uses of gene editing could contribute to further intensification of the sectors and disadvantage less intensive producers such as many of those in LMICs. Gene editing could also be valuable for producing polled cattle and eliminating the need for mechanical dehorning as currently occurs in many locales, particularly if the gene editing approaches could be utilised in local or indigenous breeds. However research in HICs has noted that public views on polling using gene editing are not as positive as might be imagined, and so reception of these uses of gene editing would need to be carefully considered.

In summary, the widespread development and application of gene editing for animal welfare purposes is unlikely to occur in LMICs in the short- or medium-term because of the mismatch between the traits likely to be targeted and those of concern, the production systems most common in those locales which are often not vertically integrated and/or rely on local or indigenous breeds, higher numbers of smallholder farmers in these locales, the cost of these technologies, the relative lack of investment by companies or NGOs to the use of gene editing in livestock in LMICs, limited focus by gene editing researchers on LMICs, and the lack of local biotech and related training and resources in many of these locales. Although gene editing has been claimed to be a relatively democratic technology, its application nonetheless requires certain standardised breeding systems and other conditions, and a considerable amount of know-how and resources, which are not present in most LMICs.

Although there are limited regulatory barriers or religious limitations associated with gene editing of livestock in many LMICs and in fact some supportive mechanisms such as investment provided via government in locales such as India, there may be other drivers that would lead to barriers to the use of gene editing in LMICs, including concerns about who benefits similar to what occurred in debates over GM crops. In addition, there is growing awareness of the value of the genetic diversity represented in traditional and indigenous breeds, and the need to protect it. It is possible that gene editing research could focus on well-adapted indigenous livestock breeds which might result in identification of important traits that could be transferred to commercial breeds using gene editing and other technologies, and which in turn might support continued coexistence of diverse breeds and types of agricultural systems.

Perhaps most importantly, many of the animal welfare issues associated with livestock used for production in LMICs are unlikely to be best addressed through applications of gene editing. For some traits associated with animal welfare, it may be that greater genetic improvements can be made through more traditional breeding techniques. It also is clear that considerably more efforts should be placed on lower tech measures such as better access to veterinary services, better training about handling of animals, increased biosecurity measures, and poverty reduction initiatives which can improve the general conditions of life for both humans and livestock animals.

Perhaps most importantly, many of the animal welfare issues associated with livestock used for production in LMICs are unlikely to be best addressed through applications of gene editing.

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