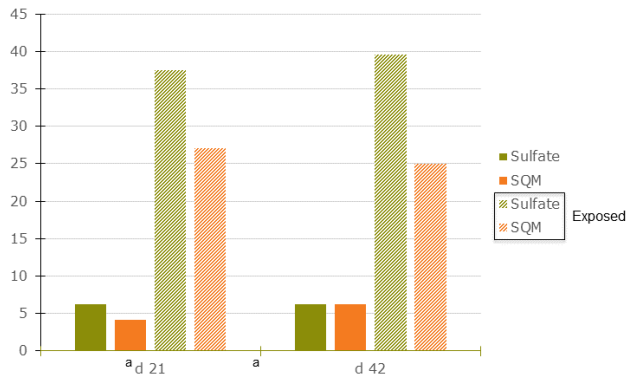
Iron regulation in poultry under *Salmonella* infection

Introduction

Maximized performance in animal production requires optimum health status. The phasing out of antibiotics as growth promoters, and the restricted use of antibiotics for therapeutic interventions, have created the need for new tools to minimize gut pathogen growth. Even low level of colonization by pathogenic microbes can cause "subclinical" infections, which can result in considerable loss of profitability to producers, as they observe suboptimal performance but are unable to determine the root cause of the problem.

The vast majority of pathogenic microbes have a high requirement for iron to augment their growth rates. Kochan (1973) coined the phrase "Nutritional Immunity" when describing how host metabolism will act to sequester free iron during infection. More recently, QualiTech has demonstrated that SQM® Iron can support animal growth at the expense of potential pathogens, by altering microbial access to complexed iron via SQM PolyTransport Technology™. A summary of these SQM Iron effects specific to Salmonella growth is shown in Figures 1-3. Additional information on SQM Iron effect on pathogen growth can be found here: https://www.qualitechco.com/sqm-poultry/

Figure 1: Iron source during microbial exposure
Salmonella prevalence, %

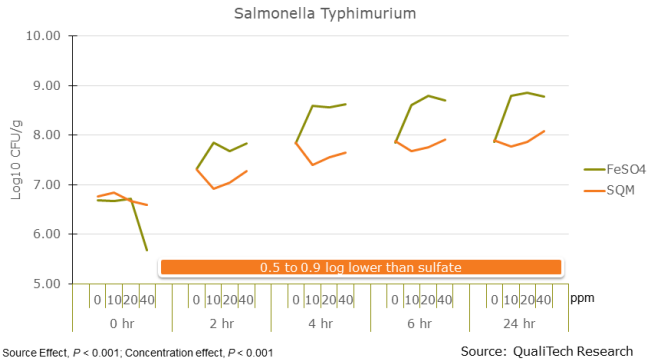


[a] Exposure effect $P < 0.01$

Source: QualiTech Research

TID: 2018-02

Figure 2: Iron source and microbial growth
University of Minnesota

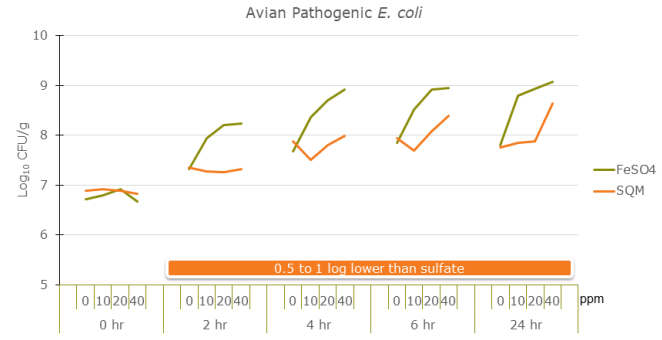


Source Effect, $P < 0.001$; Concentration effect, $P < 0.001$

Source: QualiTech Research

TID: 2020-07

Figure 3: Iron source and microbial growth
University of Minnesota



Source Effect, $P < 0.001$; Concentration effect, $P < 0.001$

Source: QualiTech Research

TID: 2020-07

Iron absorption by the host

Knowledge about the mechanisms by which iron interacts with pathogens and host continues to evolve. A recent review by Tan et al. (2021) summarizes the current understanding of iron homeostasis in poultry in the context of *Salmonella* infection scenarios. Figure 4 (adapted from Tan et al., 2021) illustrates how host enterocytes manage the flow of iron, while balancing the need for iron and the need to prevent iron from undesired side reactions. In the Apical membrane, DcytB converts Fe^{3+} to Fe^{2+}, as poultry can only absorb iron in the Fe^{2+} state. The Fe^{2+} is then absorbed by the DMT1 symporter. Additionally, the enterocyte has the ability to absorb heme via the HCP1 transporter.

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Once Heme is inside the cell, it is degraded by HO-1 and HO-2 to free Fe^{2+}, which is then stored in ferritin. Excess Fe^{2+} and Heme are exported into the blood via the FPN1 and FLVCR1 transporters in the basolateral membrane. Hephaestin then transform Fe^{2+} to Fe^{3+} for attachment to the chaperone protein transferrin (holo-Tf = unbound, diferric-Tf = bound). In this form (diferric-Tf) iron can be safely transported to other tissues.

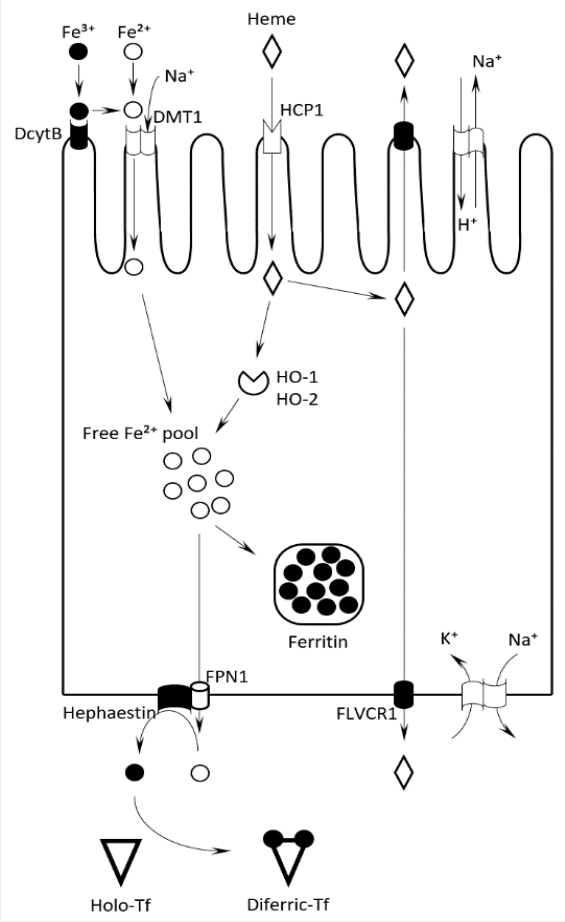

Figure 4. Iron absorption in the broiler chicken (adapted from Tan et al., 2021).

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Response to *Salmonella* infection

According to Tan et al. (2021), birds will respond to infection by upregulation of Hepcidin, which will in turn bind to and degrade FPN1, thus reducing net transport of Fe^{2+} into the blood. Pro-inflammatory cytokines will modulate the function of the apical membrane protein DMT1, to reduce the flow of Fe^{2+} into the enterocyte as Hepcidin is reducing the flow out. Cytokines will also increase the production of Transferrin, thus reducing the amount of free Fe^{3+} in the blood.

Furthermore, macrophages – tasked with phagocytizing and degrading *Salmonella* – will also attempt to deny *Salmonella* access to iron (Figure 5). In response to pro-inflammatory cytokines expression of the macrophage transferrin receptor, which is normally involved in iron absorption, will be reduced in the plasma membrane. In addition, Nramp1 (pH dependent transporter) will increase export of iron from the phagosome, thus depleting the Fe available to already phagocytized *Salmonella*.

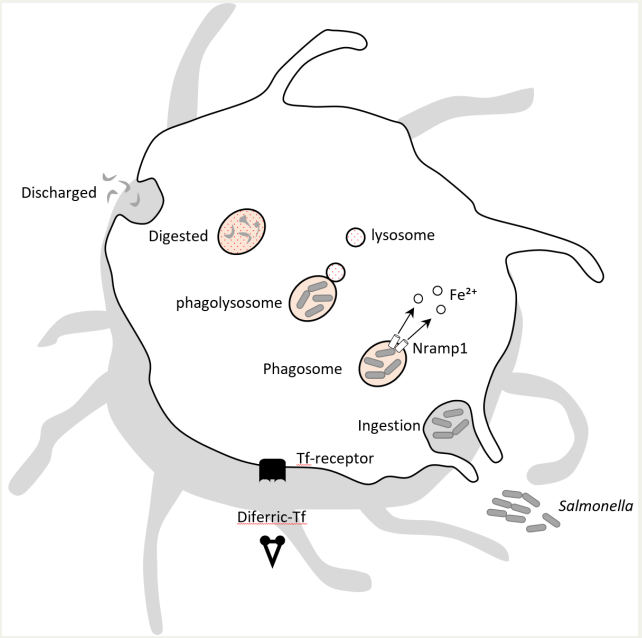

Figure 5. Modulation of iron metabolism in macrophage during *Salmonella* infection

All that effort, for what?

So this begs the question, why does the immune response to *Salmonella* infection have so many different responses that all result in sequestration of iron? The answer is that iron plays an important role in the ability of *Salmonella* to establish and maintain an infection. By reducing the availability of this essential nutrient to the pathogen, the bird is protecting itself and improving its own prospects for survival and growth. SQM® Iron is an effective tool to manage this process, by maximizing iron availability to the animal while restricting pathogen access to iron, thereby supporting optimized animal health and performance.

Garrett, J. & McNaughton, J. (2019) *Poultry Science 98(E-Supplement 1)* 555P
Kochan, I (1973) *Curr Top Microbiol Immunol*. 1973;60:1-30. doi: 10.1007/978-3-642-65502-9_1.
Tan, Z., et al. (2021) *J. Appl. Poult. Res.*, 30(1), 100101.