Received: 22 April 2020 | Accepted: 27 May 2020

DOI: 10.1002/jmv.26100

REVIEW

JOURNAL OF MEDICAL VIROLOGY WILEY

The long-standing history of *Corynebacterium parvum*, immunity, and viruses

Beniamino Palmieri[1,2] | Maria Vadalà[2] | Luca Roncati[3] | Andrea Garelli[4] | Francesco Scandone[5] | Moreno Bondi[6] | Claudio Cermelli[7]

[1]Department of General Surgery and Surgical Specialties, Surgical Clinic, University of Modena and Reggio Emilia Medical School, Modena, Italy

[2]Clinical Research Department, Second Opinion Medical Network, Modena, Italy

[3]Department of Pathology, University Hospital of Modena, Modena, Italy

[4]Department of Plastic and Reconstructive Surgery, Tor vergata's University, Roma, Italy

[5]Anesthesiology and Reanimation Department, AUSL, Avellino, Italy

[6]Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy

[7]Dental Department of Morphological Sciences Related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

Correspondence
Maria Vadalà, Clinical Research Department, Second Opinion Medical Network, Modena, Via Ciro Bisi, 125, 41124, Italy.
Email: mary.vadala@gmail.com

Abstract

We report a review of all the experimental and clinical studies performed in the last 60 years on the antiviral activity of inactivated *Corynebacterium parvum (Cutibacterium acnes)*. This bacterium has been originally investigated and used for its oncolytic properties linked to immunomodulating activity, but the interest to successfully prevent and treat bacterial, fungal, and viral infections and lethality, uprising the innate immunity barriers produced many experimental models and very few clinical studies. The dramatic defenseless situation due to impending CoViD-19 pandemic claims to exhume and highlight this aspecific strategy in preventive and therapeutic settings; as a matter of fact, no new or mutated virus can potentially escape to this strong innate immune surveillance strengthened by adequate *C. parvum* protocols.

KEYWORDS

C. parvum, coronavirus, immune responses, immunomodulation, innate immunity

1 | INTRODUCTION

Cutibacterium acnes (formerly known as *Propionibacterium acnes or Corynebacterium parvum*) has been widely investigated as far as the skin microbiota environment.[1] In 1900, it was identified as *Bacillus acnes*[2]; in the following years, because of its club-shaped appearance it was classified as *Corynebacterium*, but, its mainly anaerobic metabolism and biochemical characteristics were more similar to propionic acid bacteria.[3] For this reason, the name *Propionibacterium acnes* (*P. acnes*) was successfully maintained up to 2016, when it was reclassified as *Cutibacterium acnes* due to peculiar genomic adaptive changes.[4]

P. acnes is a Gram-positive anaerobic bacillus that belongs to the normal cutaneous microbiota provided of immunomodulatory activity when used as a heat- or phenol-killed suspension.[5] Among its main biological activities, *P. acnes* promotes macrophage activation,[6,7] displays oncolytic properties,[8-10] and is an effective adjuvant when added to normal vaccines-enhancing soluble and cell-mediated immune response;[11,12] all these properties boost up the infection resistance observed after intraperitoneal or subcutaneous administration.[13-16] The mechanisms responsible for the modulating effects of *P. acnes* on both innate and acquired immunity are mediated by interferon and proinflammatory cytokines, and are related on Toll-like receptor 2 (TLR2), Toll-like receptor 9 (TLR9), and Myeloid differentiation primary response 88 (MyD88) receptors[17-19]; they also enhance the Th1 population function.[20,21]

The experimental in vitro/in vivo and clinical studies on immunomodulating properties of *C. parvum* go back to 1964 when Halpern first discovered and published his experience of reticuloendothelial stimulation by *C. parvum* injection, with enlargement of spleen and liver that reverted after the peak at 14 day, and whose reticuloendothelial hyperplasia cleared quickly intravenous delivered carbon particles.[6]

1.1 | Experimental studies on immunomodulating properties of *C. parvum*

In 1966, the same author and coworkers demonstrated that mice pretreated with *C. parvum* were refractory to priming of tumor cells transplant.[8]

In 1977, Geniteau et al[22] published a paper, entitled: *Effect of Corynebacterium parvum on various viral infections in the mouse.*

In the same year, Glasgow et al[23] injected *C. parvum* in mice 7 to 10 days before inoculation of herpes simplex virus hominis type 2 (HSV-2), Murine encephalomyocarditis virus (EMCV), murine cytomegalovirus virus (MCMV), and Semliki Forest Virus. The different groups of animals were highly protected against lethal infections. In the encephalomyocarditis experiment, the virus infection was counteracted either by the intraperitoneal, or the respiratory route of *C. acnes* administration, with a systemic, rather than local effect.

C. acnes was not effective in new borne animals, probably requiring maturation of the soluble- and cell-mediated immune responses. The lymphoreticular system played a central role as demonstrated by transfer of enhanced resistance against HSV-2 to recipient animals infused with peritoneal exudate cells harvested from *C. acnes*-pretreated mice. The same cells inhibited in vitro the herpetic virus colonization into target cells. In this experimental study the activated macrophages were the key of immune modulating resistance to viral infections.[23]

Also, Kirchner et al[24] reported protective effect of *C. parvum* in normal and immunosuppressed mice. In this same year, Szmigielski et al[25] demonstrated that the intraperitoneal injection of *C. parvum* in HSV-2 encephalomyelitis reduced the mortality rate from 90% to 30%. The same author neutralized the mortality of varicella and hepatitis B Virus (HBV) infection in proper experimental models.[26]

Papaevangelou et al[27] investigated the immune potentiating effect of the intradermal administration of four doses (0.25 mL) of a standard suspension of killed *C. parvum* (2 mg/mL) in 10 asymptomatic chronic Hepatitis B surface antigen (HBsAg) carriers, compared with 11 persons with antibodies to HBsAg (anti-HBs) and six without HBsAg or anti-HBs.

HBsAg, anti-HBs, and leukocyte migration inhibition studies were performed in pre-and postinoculation blood samples. *C. parvum* produced a substantial increase of anti-HBs titer in persons with preexisting anti-HB immunity. However, anti-HBs responses were not induced in carriers. HBsAg was not eliminated and its titer remained practically unchanged in chronic carriers. The conclusive hypothesis is, that the specific defect in the immune response to HBsAg in carriers ought to be at the B cell level.

Kobus and Szmigielski demonstrated that subcutaneous *C. parvum* injection simultaneously with live attenuated viral vaccines achieved an higher immunity rate and protection in several experiments.[28] Teixeira et al[29] evaluated the adjuvant role of *C. parvum* in BALB/c mice with HIVBr18, a DNA vaccine containing 18 $CD4^+$T cell epitopes from human immunodeficiency virus (HIV), specifically and steadily uprising the $CD4^+$ and $CD8^+$T cell responses. The *C. parvum* added to vaccine administration increased the proliferation of HIV-1-specific $CD4^+$ and $CD8^+$T lymphocytes, the polyfunctional profile of $CD4^+$T cells, the production of interferon gamma (IFN-γ), and the number of recognized vaccine-encoded peptides; the immunological reinforcement was more striking using the whole dead *C. parvum* as adjuvant compared with its bacterial polysaccharides extract; IFN-γ production as well as T cells proliferation were maintained up to 10 weeks after the challenge with the whole dead bacterium.[29] Since it has been successfully used as an adjuvant in experimental trials, *P. acnes* can be a suitable candidate for integration in human vaccines to enhance the immune response.[30,31]

Moreover, Budzko et al[32] showed a dose-dependent response in Junin virus infection in mice: 280 mcg injected intraperitoneally uplifted the survival rate to 80% compared with 20% of the untreated animals. Naficy et al[33] reported the antiviral activity of five different *C.parvum* strains in comparison with simple vaccination, stressing an effective adjuvant role. Also the French researcher Cerutti[34] demonstrated the antiviral/protective activity of *C. parvum* against lethal infections of Newcastle disease virus (NDV), EMCV, and vesicular stomatitis viruses (VSV) in mice experimental models.

Schindler et al[35] observed a protective effect when *C. parvum* was given 2 hours before or 2 hours after viral infection with mouse hepatitis virus (MHV) a Coronavirus strain 3 (MHV-3).

He suggested also that *C. parvum* determined a significant decrease of virus yield in cultures of peritoneal exudate cells infected with MHV3. He showed that contemporary intraperitoneal injection of the virus and of *C. parvum* prevented the infection with activation of interferon and natural killer cells but also with a direct action upon macrophages who are the primary target of virus replication. In fact, Belyavsky et al[36] demonstrated that Coronavirus MHV-3 produces fulminant lethal infection in fully susceptible BALB/c mice with massive-apoptosis in macrophages that play a key role in the virus induced liver failure.

Mak et al[37] showed that intranasal administration of 350 μg *C. parvum* 3 days in advance protected different mice strains (c57BL/6j, BALB/CBalb/cnu+NU+) from influenza lethality. A substantial reduction of the intrapulmonary copies of virus was detected in parallel to the level of interferon and macrophage activation in the lung. Despite the increase in macrophage content, the level of specific immune responses to infection, such as cytotoxic T-cell activity, delayed-type hypersensitivity reaction, and antihemagglutinin antibody, remained unchanged by *C. parvum* treatment so that the major if not exclusive effect of this treatment was supposed to be an uplift in the general components of the immune system.

Zgórniak-Nowosielska et al[38] achieved strong resistance against vaccinia viruses and Herpes Virus-1 with *C. parvum* pretreatment. Splenomegaly was induced by the procedure, but the specific antibodies titer was unchanged suggesting enhancement of natural immunity rather than specific soluble immunity stimulation.

Kounoue et al[39] prevented the virus induced encephalomyocarditis of mice with a 3 to 14 tailored pretreatments of *C. parvum*; this therapy prevented pancreas colonization by virus, causing insulae destruction and diabetes. Cohen et al[40] treated ectromelia virus-infected mice with intraperitoneal *C. parvum* in comparison with mineral oil adjuvant

injection. The protection was obtained through macrophage uptaking and killing of the viruses and interferon induction.[40] Mayr et al[41] evaluated in vitro and in vivo the immunomodulation activity of levamisole, BCG, and *C. parvum* in viral and bacterial infections outlining a superior activity of both the bacteria compared with the synthetic drug. Cox (1998) used *P. acnes* to treat cat's anemia due to Feline Leukemia Virus (FeLV) infection. He obtained a marked improvement of erythrocyte and leukocytes, compared with the untreated group. The same American researcher Cow with the researcher Weiss[42] investigated also in the cat viral peritonitis model treatment with interferons (IFNs) and *C. parvum* (either single or joined administration) different dosages for prevention or therapy. Notwithstanding the high lethal dose of virus, the survival rate of the group treated with interferon or interferon plus *C. parvum* was much higher than in the control untreated group. Hall et al[43] treated bovine papilloma virus (BPV) infections with local infiltrations of *C. parvum*; the animals healed definitely in 15 weeks.

Flaminio et al[44] evaluated in healthy young horses the immunological impact of three injections of *C. parvum* either in blood and in bronchoalveolar lavage (BAL) at 0, 7, and 14 days.[44] Total peripheral blood white cell count was increased ($P < .05$) at 14 day. l BAL fluid cell count decreased ($P < .01$) on day 14 due to lymphocyte ($P < .01$) and macrophage ($P < .01$) reduction with an inversion of lymphocyte/macrophages ratio; total ($P < .05$) and proportional ($P < .05$) counts of $CD4^+$T lymphocytes were increased in the peripheral blood. On day 14, bronchoalveolar lavage fluid proportion of $CD4^+$ ($P < .05$), $CD5^+$ ($P < .001$) and major histocompatibility complex class II (MHC II) ($P < .05$) lymphocytes increased as well; nonopsonized phagocytic activity in peripheral blood increased ($P < .0005$); lymphokine-activated killing cell activity in peripheral blood and BAL fluid leukocytes was enhanced ($P < .005$). Serum IgG and IgM remained unchanged. This investigation demonstrated the immunostimulant and modulatory properties of *P. acnes*, by increased $CD4^+$T lymphocyte expression and lymphokine-activated killer (LAK) activity in peripheral blood and BAL fluid, by increased nonopsonized phagocytosis in peripheral blood leukocytes but with reduced number of live cells in BAL.

Megid et al[45] dealing with dogs in veterinary setting, affected by oral papillomatosis, a virus-induced pathology of the mouth, at different ages achieved complete regression after five average weekly injections of *C. parvum*, locally delivered.[45] The same author (2002) examined in the rabies infected swiss mice the lethality and distribution of the virus copies comparing the plain vaccination versus vaccination + *C. parvum*.[46] The survival rate was higher in the *C. parvum* added treatment group, and it was related to a greater number of viruses sequestration into the spleen and lymph node macrophages.

Megid, 1 year before, had measured the natural killer (NK) activity and lethality in the same mice model exposed to rabies virus and treated with *C. acnes*; the mice were progressively killed and the spleen cells rescued and analyzed.[47] Higher NK activity and better survival rate were observed in the *P. acnes* cohort outlining this lymphocyte population as the key mechanism of rabies virus neutralization. In a mouse model of vaccination, the same author (2006) analyzed the cytokines response to rabies vaccine propagated in VERO cells, compared with the same vaccination procedure plus *C. parvum* or *C. parvum* alone.[48] The highest survival was achieved with one or two doses of *P.acnes* alone: on the contrary antirabies VERO vaccine alone or with three doses of *P. acnes* survived at a lesser rate. The mortality was directly related to the highest IL-6 concentration accordingly with the clinical symptoms. Obviously, *P. acnes* counteracted the IL-6 overexpression in the rabies model being this cytokine responsible of the mice mortality. Davis et al[49] successfully administered *C. parvum* in horse tracheobronchial viral infections, detecting increased blood levels of interferon, monocytes and killer lymphocytes in parallel to the symptoms relieve. Caney[50] reports the current professional veterinary use of *C. parvum* as immunomodulator especially effective in FeLV with anecdotal reports of curing the affected cats.

Paillot[51] reviewed the immunomodulation properties of inactivated Parapoxvirus Ovis (iPPVO) and *P. acnes* for prophylactic treatment of bronchopulmonary infections usually of viral origin in horses. The action mechanism relies on a non–antigen specific interaction with the innate and/or adaptive immune responses. iPPVO stimulates and regulates cytokine secretion by leukocytes, while *P. acnes* acts primarily through the activation of macrophages; in the author's opinions, both immunomodulators can be profitably added to conventional antibiotic therapy or vaccination. Vail et al[52] added *P. acnes* to conventional therapy of Equine Respiratory Disease Complex (ERDC). A first group of 25 horses received conventional therapy + *C. parvum* and a second group of 20 horses (negative controls) received conventional therapy plus 12.5% ethanol-saline solution. Two weeks later, 96% (24/25) of the horses treated with *C. parvum* and conventional therapy underwent full recovery or clinical improvement; while in the control group only 35% (7/20) showed clinical improvement or complete recovery. Adams et al[53] performed a study on weaning horses, usually severely distressed in that life period, with reduced immunity and increased susceptibility to gastrointestinal and respiratory disorders. Thus, preventative administration of immunomodulator aimed at mitigating the weaning-associated stress was studied in 21 pony foals (205 days ± 5-day-old). Of these, 11 animals received the *C. parvum*-based immunostimulant EqStim and other (n.10) received a saline control on days −7, −3, and 0 (day of weaning). At days 3, 7, 14, and 21, the following clinical parameters were measured: cortisol, immune function by flow cytometry, and real-time polymerase chain reaction (PCR) for gene expression, and nasal swabs (NSs) and C reactive protein (polymerase chain reaction, PCR). Results showed an overall time effect of weaning for most parameters: decreased rectal temperature, increased nasal discharge, and NS PCR detection of *Streptococcus equi* subsp. *zooepidemicus*, increased serum cortisol levels, and both decreased and increased production of cytokines (lymphocyte production interferon gamma and tumor necrosis factor alpha (TNF-α) and whole blood levels of Interleukin 1 beta (IL-1β), TNF-α, and Interleukin 10 (IL-10). In addition, there was an increase on cortisol concentrations and peripheral blood mononuclear cell production of IL-1β. These data suggest that, regardless of treatment, the weaning process produces significant changes in clinical and immunologic measures in foals.

1.2 | Clinical studies on immunomodulating properties of *C. parvum*

Coming to clinical trials, Nasser[54] treated 20 patients severely affected by multiple common warts infections (caused by different strains of papilloma virus) with repeated local injections of *C. parvum*, 0.2 mL subcutis (10 patients) compared with placebo (saline solution).[44] The procedure was repeated from 1 to 5 months dependently by the regression rate and it was definitely effective in 9 cases out of 10, with partial regression in the last one but none of the placebo group had any benefit except one partial regression.

Our literature search was not able to find in the past any human trial or anecdotal report on *C. parvum* treatment of viral infections except the contribution of Papaevangelou et al[27] and Nasser[54] (see above).

Forty years ago, Palmieri et al[55] during some clinical trials on cancer-bacteria immunotherapy had the chance to successfully use dead *C. parvum* primarily in severe zoster infections occasionally coaffecting three cancer patients. The *C. parvum* intratumor injection very quickly suppressed the infections. This serendipitous finding disclosed the hypothesis of treatment benefits on a wider viruses range. The injection protocol varied from 2 mL of dry lyophilized bacterium subcutis each other day for three sessions, to five sessions following the course of the infection.

These positive antivirus results were even more striking because no Herpes suppressing drug was market available at that time (except the weakly effective lysozyme).

The author subsequently followed up growing *C. parvum* in the hospital facilities and treated anecdotally further patients with severe impending common viral infection symptoms (including huge skin eruptions, vesical mucositis, high fever, lymph nodes and salivary glands enlargements bronchopulmonary complications, etc). All the viral infections, such as herpes simplex (n = 12), herpes zoster (n = 12), influence (n = 4), mumps (n = 2), varicella (n = 2), and measles (n = 3) subsided very quickly. The recovery was safe and quick, with fever and symptoms downstaging after 18 to 72 hours; no relevant side effects of the procedure were detected and the remission of neurological, respiratory, cardiovascular, cutaneous and fatigue symptoms overall satisfactory.

2 | DISCUSSION

Corynebacterium parvum is the protagonist of a unique long-standing international publications series reporting its peculiar immunomodulating role against a wide variety of virus infections, and mortality (Table 1) either in experimental lab or in domestic animals. Its wide spectrum antiviral activity is supposedly due to an aspecific activity potentiating monocytes, and natural killer cells with regard to their number and function, and interferon gene activation; this is the basic very first barrier to virus invasion, a mechanism confirmed by a great number of experimental studies on different animal species.

Thus *C. parvum* antagonism against virus infections is projected either in neutralizing virus-induced cell dysfunction and death (for instance respiratory epithelium, hepatocytes, dendritic macrophages, etc), or in counteracting the antivirus-triggered inflammatory cytokine cascade turning an endogenous defense weapon into a self-destructive lethal mechanism.

Kalis et al[18] focused primarily on the bacterium-host immune cell interaction to better understand the immunomodulating mechanisms of killed *C. parvum* preparation through systemic and organ specific (lung) innate immunity: The receptor type involved in this interaction is Toll-like receptor 9 (TLR9). As a matter of fact, $TLR9^{-/-}$ clock out mice, *C. parvum* stimulation is not able to induce either splenomegaly and extra bone marrow hemopoiesis, or TNF alfa and interferon gamma (based on Modulation of IFN-γ mRNA expression) productions; also resistance to murine typhoid fever morbidity and mortality fails in *C. pavum* immunized $TLR9^{-/-}$ mice based on this investigation. The promyelocytic dendritic macrophages, migrating class of monocytes plasmacytoid DCs (pDCs) represent 0.2 to 0.8% of peripheral blood mononuclear cells and display plasma cell morphology in humans.[56] They express only TLR7, 8 and 9, but not TLR2, TLR3, TLR4 and TLR5. Therefore, they are supposed through TLR9 and TLR7 to play a primary role in DNA and RNA virus to some DNA and RNA viruses, preventing the infections either shaping and upgrading innate immunity, or translating the innate response to adoptive immunity.[56] pDCs produce massive amounts of type I interferon, activating NK cells, NKT cells, B cells, T cells, and myeloid uncommitted DCs and then complete the suppression and clearance of the virus particles.[57] *C. parvum* probably recruits and activates these cells with chemotactic signal, enhancing the defense against viruses.

We suppose that in humans, as in the experimental animal models, the dead bacterium acts initially as a strong TLR9 agonist, activating macrophages and promoting high levels of Th1, TNF, interferon, and natural killer cells to clear the infecting pathogens.

Another intriguing interplay between viruses and *C. parvum* is the pivotal role of vimentin. We know from dermatological investigations that inflammation of sebaceous glands and keratinocytes by *Cutibacterium acnes* involves a complex cytokines cascade, and that live *C. acnes* enters into monocytes and tissue cells and can survive and proliferate interacting with vimentin network, a component of the cytoskeleton.[58,59] *P. acnes* invades the prostate cells that express vimentin, which is able to activate immune response against the bacterium through the Nuclear factor-κB (NFkB) intracellular innate immune signaling.[60]

Also, several viruses, for example severe acute respiratory syndrome coronavirus (SARS-CoV) and Enterovirus 71,[61-63] like *C. parvum* interact with vimentin on the cell membrane surface; vimentin acts as virus receptor promoting endocytosis, trapping pathogenic agents, and finally triggering the NFkB pathway. Subsequently, after the inflammatory reaction, we find extracellular vimentin extruded from activated macrophages, to definitely remove the infectious agents. The virulence of intracellular surviving viruses and bacteria can further be expressed by their enzymatic modification and intracellular distribution of vimentin filaments, neutralizing its defense function.

TABLE 1 Description of studies on *C. parvum*

No.	Study type	Virus type	Aim	Results	References
#1	In vivo study	-*Mycobacterium tuberculosis*, BCG or saprophytes, eg, *M. phlei*,	Stimulation of macrophages and fagocitary activity after *Corynebacterium parvum* (*C. parvum*) injection	He confirmed of reticuloendothelial stimulation by *C. parvum* injection, with enlargement of spleen and liver that reverted after the peak at 14 d.	Halpern et al[6]
#2	In vivo study	-Epithelioid sarcoma	The effect of *C. parvum* on tumors of sarcomatous or epithelial origin	He demonstrated that *C. parvum* pretreated mice were refractory to challenge of tumor cells	Halpern et al[8]
#3	In vivo study	-Several viruses	Antiviral properties of five strains of *C. parvum*	...	Naficy et al[33]
#4	In vivo study	1. NDV 2. EMCV 3. VSV	Therapeutic effect of *C. parvum* in infected mice	He verified the antiviral/protective activity of *C. parvum* against lethal NDV infections, encephalomyocarditis, and vesicular stomatitis viruses in mice experimental models	Cerutti et al[34]
#5	In vivo study	-Several viruses	Effect of *C. parvum* on various viral infections in the mouse	...	Geniteau et al[22]
#6	CLINICAL TRIAL	-Hepatitis B	The immunopotentiating effect of the intradermal administration of killed *C. parvum* (four doses) in 27 patients: 10 asymptomatic HBsAg, 11 persons with anti-HBs, and 6 without HBsAg or anti-HBs.	The author hypothesized that in carriers the specific defect in the immune response to HBsAg probably exists at the B cell level.	Papaevangelou et al[27]
#7	In vivo study	-EMCV-1	Effect of *Corynebacterium acnes*, *C. parvum* and *bacilli Calmette-Guèrin* in mice infected with EMCV-1	The cells of the lymphoreticular system inhibited the progression of herpetic infection in tissue culture, possibly through activation of macrophages	Glasgow et al[23]
#8	In vivo study	-Junin virus	The effect of intraperitoneal *C. parvum* administration in mice infected with Junin virus	The data showed that the symptoms, in mice, were not the consequence of cell damage caused directly by the virus but of a undefined indirect mechanism induced by the virus, not necessarily mediated by macrophages.	Budzko et al[32]
#9	In vivo study	-HSV-1	Effect of *C. parvum* and *Bordetella pertussis* in mice infected with HSV-1	The authors suggested that intraperitoneal (IP) injection of killed *C. parvum* (10 mg/kg) 1 wk before IP infection of adult mice with HSV-1 protected them from encephalitis and death. The data evidenced high levels of interferon in the serum of mice injected with *C. parvum* 5 to 12 d previously.	Kirchner et al[24]
#10	In vivo study	-Guèrin tumor	Effect of *C. parvum* injection into the Guèrin tumor	The author observed a synergistic effect with heat (43°C for 60 min) that resulted in augmented tumor regression and increased macrophage activity against the tumor cell in vitro	Szmigielski[25]
#11	In vivo study	1. Herpes simplex, 2. VACV, 3. MHV-3	Effect of *Propionibacterium granulosum* kp-45 in BALB/c mice infected with three different viruses (herpes simplex, VACV, and mouse hepatitis)	The data showed a significant lowering of the number of paralysed mice and in a decrease of the mortality rate.	Szmigielski et al[26]

(Continues)

TABLE 1 (Continued)

No.	Study type	Virus type	Aim	Results	References
#12	In vivo study	-MHV-3	Protective effect of intraperitoneal *C. parvum* injection in MHV-3-infected susceptible C57Bl/6 mice	The author observed an effect when *C. parvum* was given 2 h before or 2 h after viral infection. He suggested also that *C. parvum* determined a significant decrease of virus yield in cultures of peritoneal exudate cells infected with MHV3	Schindler et al[35]
#13	In vivo study	-Influenza virus	Effect of intranasally *C. parvum* inoculation (350 μg/mouse) in C57BL/6J, BALB/c, BALB/c, nu+/nu+ mice	He showed that protected different mice strains from influenza lethality	Mak et al[37]
#14	In vivo study	-ECTV	Effect of intraperitoneal *C. parvum* in comparison with mineral oil adjuvant injection in ectromelia virus infected mice	The protection was obtained through macrophage uptaking and killing of the viruses and interferon induction	Cohen et al[40]
#15	In vivo and in vitro study	1. VSV and Aujeszky virus. 2. Tumor model (radiation induced osteosarcoma in the mouse)	Effect of individual immunostimulants (*C.parvum*, BCG, and levamisole)	The immunomodulation activity of these components in viral and bacterial infections outlined a superior activity of both the bacteria compared with the synthetic drug	Mayr et al[41]
#16	In vivo study	EMCV induction of diabetes mellitus	Effect of *C.parvum* in encephalomyocarditis virus-induced diabetes in mice	The *C. parvum* inoculation given 3-14 d before the virus infection inhibited the virus replication in the pancreas of the mice	Kounoue et al[39]
#17	In vivo study	1. VACV, 2. HSV-1	Effect of *Proprionibacterium acnes* (formerly *C. parvum*) in infected mice	The data achieved strong resistance against VACV and HSV-1 with *P. acnes* pretreatment	Zgòrniak-Nowosaelska et al[38]
#18	In vivo study	-Equine respiratory disease complex (ERDC)	Effect of *P.acnes* (Eqstim) treating horses with ERDC	The authors treated 25 horses with Eqstim and 20 with conventional therapy. The 96% of the horses of the first group showed clinical improvement or complete recovery	Vail et al[52]
#19	In vivo study	-Feline infectious peritonitis virus (FIP-V)	Effect of *P.acnes*, interferon, and combination of these drugs in 74 cats infected with FIPV	The survival rate of the group treated with interferon or interferon plus *C. parvum* was much higher than in the control untreated group.	Weiss et al[42]
#20	In vivo study	-BPV	Evaluation od *C. parvum* suspension in BPV	The data showed that intralesional administration of *C. parvum* induced regression of bovine papillomas in 8-15 wk	Hall et al[43]
#21	In vivo study	-HSV-1	Effect of heat-killed lyophilized *Propionibacterium avidum* KP-40 (PA) and/or the herpes-specific antiviral substance acyclovir (ACL) as immune-modifier in NMRI mice with HSV-1	The *P.avidum* applied 4 d before HSV-1 infection lowered the mortality rate to 27%, while treatment 2 d after infection was less effective and the mortality rate reached 44%, but it was significantly lower ($P < .01$) than in untreated controls. A combined treatment with *P. avidum* and protected 93% of animals against the development of encephalitis.	Kobus et al[28]

TABLE 1 (Continued)

No.	Study type	Virus type	Aim	Results	References
#22	In vivo study	-Respiratory disease	Evaluation of inactivated *P. acnes* (Eqstim) in horses	The data confirmed immunostimulant and immunomodulatory properties of *P. acnes*, evidenced by increased $CD4^{+}$T lymphocyte expression and LAK activity in peripheral blood and BAL fluid, increased nonopsonized phagocytosis in peripheral blood leukocytes and decreased pulmonary cellularity.	Flaminio et al[44]
#23	In vivo and vitro study	-MHV-3	Evaluation of macrophages role in the pathogenesis of MHV-3-induced hepatitis.	The results evidenced that murine coronavirus MHV-3 could be a RNA-containing viruses capable of inducing apoptosis.	Belvasky et al[36]
#24	In vivo study	-Rabies virus	Evaluation of treatment with the immunomodulators onco-BCG, avridine and *P. acnes* in mice with rabies virus and then inoculated with Fuenzalida-Palacios mouse brain human rabies vaccine	The results showed higher levels of IFN-gamma in the mice treated with *P. acnes*.	Megid[69]
#25	In vivo study	-Street rabies virus	Immunomodulation of *P. acnes* in swiss mice experimentally infected with street rabies virus	The data evidenced higher Natural killer activity and percentual of survival were observed in mice submitted to *P. acnes*.	Megid & Kaneno[47]
#26	In vivo study	-Canine oral papilloma	Effect of *P. acnes* in 16 dogs with oral warts	These results suggested the use of *P. acnes* as an alternative in these symptoms	Megid et al[45]
#27	In vivo study	-Street rabies virus	Immunomodulant effect of *P. acnes* in swiss mice infected with street rabies virus and then vaccinated	The mice vaccinated and after treated with *C. parvum* presented a superior percentage of survival to that observed in mice treated only with *P. acnes*	Megid et al[46]
#28	In vivo study	…	Immunomodulant action of *C. parvum* in healthy horses	The authors showed that horses treated with a *P. acnes*-based immunomodulator exhibited increased IFN-gamma and NK-lysin gene expression in peripheral blood mononuclear cells	Davis et al[49]
#29	In vivo study	-Street rabies virus	Immunomodulation of *C. parvum* in swiss mice infected by rabies virus and after vaccinated	The authors observed, in vaccinated mice treated with *P. acnes*, greater survival rates, higher IL-10 and low IL-6 serum concentration.	Megid[70]
#30	In vivo study	-FeLV	Effect of *C. parvum*, and other antiviral agents in feline infectious diseases	The author showed therapeutic effects and no side effects	Caney[50]
#31	In vivo study	-Rabies virus	Evaluation of the survival and cytokine serum concentration of rabies virus-infected mice treated with *P. acnes* in conjunction with or the antirabies-VERO vaccine.	The greatest survival was observed in animals given one or two doses of *P. acnes* in the absence of vaccination. While, the mice inoculated with antirabies VERO vaccine alone or with three doses of *P. acnes* had the second highest survival rate.	Megid et al[48]

(Continues)

TABLE 1 (Continued)

No.	Study type	Virus type	Aim	Results	References
#32	CLINICAL TRIAL	-Human papilloma virus (HPV)	Efficacy of *C. parvum* in saline solution for the treatment of skin warts in 20 patients	In nine patients treated with the *P. parvum* solution, the warts disappeared without scars and in one patient it decreased in size.	Nasser[54]
#33	Review	-Respiratory disease and other infections, such as iPPVO	The action as immuno-modulators of iPPVO and *P. acnes* for prophylactic treatment or adjunct to conventional therapy in horses	This paper summarizes the scientific literature and reports available about iPPVO and *C. parvum* use in horses, particularly in the prevention or treatment of equine respiratory diseases	Paillot[51]
#34	In vivo study	-Nasal shedding of respiratory pathogens	Immunostimulant action of *P. acnes* (EqStim) in 21 pony foals; of these 11 received the *C.parvum* and 10 received a saline control	*C. parvum* vaccination had no effect on the incidences of nasal shedding of respiratory pathogens or other clinical parameters, but raised cortisol after weaning and enhanced innate immunity.	Adams et al[53]
#35	In vivo study	-HIV	Evaluation of adjuvant action of *P. acnes* in BALB/c mice with HIVBr18, a DNA vaccine containing 18 $CD4^+$T cell epitopes from HIV	The data showed an increase of the proliferation of HIV-1-specific $CD4^+$ and $CD8^+$T lymphocytes, of the polyfunctional profile of $CD4^+$T cells, of the production of IFN-γ, and of the number of recognized vaccine-encoded peptides	Teixeria et al[29]
#36	Clinical trial	Herpes zoster, varicella, measles, mumps, influence	*P. acnes* subcut & aerosol quick and effective control of infection	The results showed quick and safe symptoms remission and recovery	Palmieri et al[55]

Abbreviations: BAL, bronchoalveolar lavage; BPV, bovine papilloma virus; EMCV, murinencephalomyocarditis virus; ECTV, ectromelia virus; HSV, herpes simplex virus; LAK, lymphocyte activated killer; MHV, mouse hepatitis virus; NDV, Newcastle disease virus; VACV, vaccinia viruses; VSV, vesicular stomatitis viruses.

On the other hand, vimentin is a ligand of pattern recognition receptors (PRRs), including Nucleotide-binding oligomerization domain-containing protein 2 (NOD2), Dectin-1, and NLPR3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 OR NOD-like receptor protein 3), and the specific virus interceptor RIG-1-like receptors (retinoic acid-inducible gene-I-like receptors, RLRs).[64-67] These PRRs, once alerted, activate the inflammasome and NF-kB cascade to destroy the hosts.[68] Pathogenic viruses, however, can try to overwhelm these defense mechanisms, inactivating the vimentin–PRRs complex by posttranslational modifications.

In this perspective, the puzzling competition between the subcutaneous injected dead *C. parvum* and virus infections plays a determinant role to balance the innate immune defense mechanisms and virulence factors.

3 | CONCLUSION

In conclusion, the long experimental history documenting a wide spectrum antiviral activity of *C. parvum* lysates, both in vitro and in vivo, besides a limited number of clinical trials, strongly supports the hypothesis that also SARS-CoV-2 virus can be effectively neutralized by this treatment, suggesting that further investigation is worth to be carried out, mainly by clinical trials. This potential aspecific anti SARS-CoV-2 activity could efficiently prevent and treat this dramatically world spreading viral disease and help the recovery of social and productive life.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

BP: Conceptualization (lead); writing–original draft (lead); formal analysis (lead); writing – review and editing (equal). MV: Writing – original draft (equal); formal analysis (equal); writing–review and editing (lead). LR: Conceptualization (supporting); review and editing (equal). Andrea Garelli: Conceptualization (equal). FS: Conceptualization (equal). MB: Writing–original draft (equal). CC: Review and editing (supporting).

ORCID

Beniamino Palmieri https://orcid.org/0000-0002-0871-138X
Maria Vadalà http://orcid.org/0000-0001-7873-5072
Moreno Bondi https://orcid.org/0000-0002-6652-9148
Claudio Cermelli https://orcid.org/0000-0003-3396-0000

REFERENCES

1. Castillo DE, Nanda S, Keri JE. Propionibacterium (Cutibacterium) acnes bacteriophage therapy in acne: current evidence and future perspectives. *Dermatol Ther*. 2019;9(1):19-31.
2. Gilchrist TC, *A bacteriological and microscopical study of over 300 vesicular and pustular lesions of the skin, with a research upon the etiology of acne vulgaris*. Johns Hopkins Hospital Report, 1900. 9: p. 409-430.
3. Douglas HC, Gunter SE. The taxonomic position of *Corynebacterium acnes*. *J Bacteriol*. 1946;52(1):15-23.
4. Platsidaki E, Dessinioti C. Recent advances in understanding *Propionibacterium acnes* (*Cutibacterium acnes*) in acne. *F1000Research*. 2018; 7:F1000.
5. Leyden JJ, McGinley KJ, Mills OH, Kligman AM. Age-related changes in the resident bacterial flora of the human face. *J Invest Dermatol*. 1975;65(4):379-381.
6. Halpern BN, Prevot AR, Biozzi G, et al. Stimulation of the phagocytic activity of the reticuloendothelial system by *Cornyebacterium parvum*. *J Reticuloendothel Soc*. 1964;1:77-96.
7. Woodruff MF, McBride WH, Dunbar N. Tumour growth, phagocytic activity and antibody response in *Corynebacterium parvum*-treated mice. *Clin Exp Immunol*. 1974;17(3):509-518.
8. Halpern BN, Biozzi G, Stiffel C, Mouton D. Inhibition of tumour growth by administration of killed corynebacterium parvum. *Nature*. 1966;212(5064):853-854.
9. Keller R, Keist R, van der Meide PH. Modulation of tumoricidal activity, induced in bone-marrow-derived mononuclear phagocytes by interferon gamma or Corynebacterium parvum, by interferon beta, tumor necrosis factor, prostaglandin E2, and transforming growth factor beta. *Int J Cancer*. 1991;49(5):796-800.
10. Kennedy JD, Sutton RC, Conley FK. Effect of intracerebrally injected Corynebacterium parvum on the development and growth of metastatic brain tumor in mice. *Neurosurgery*. 1989;25(5):709-714.
11. Warr GW, James K. Effect of Corynebacterium parvum on the class and subclass of antibody produced in the response of different strains of mice to sheep erythrocytes. *Immunology*. 1975;28(3):431-442.
12. Mussalem JS, Vasconcelos JR, Squaiella CC, et al. Adjuvant effect of the *Propionibacterium acnes* and its purified soluble polysaccharide on the immunization with plasmidial DNA containing a *Trypanosoma cruzi* gene. *Microbiol Immunol*. 2006;50(4):253-263.
13. Nussenzweig RS. Increased nonspecific resstance to malaria produced by administration of killed Corynebacterium parvum. *Exp Parasitol*. 1967;21(2):224-231.
14. Ha DK, Lawton JW, Gardner ID. The effect of in vivo modulation of macrophage activities on Mycobacterium lepraemurium infection. *J Comp Pathol*. 1986;96(5):565-573.
15. Abath FG, Coutinho EM, Montenegro SM, Gomes YM, Carvalho AB. The use of non-specific immunopotentiators in experimental Trypanosoma cruzi infection. *Trans R Soc Trop Med Hyg*. 1988;82(1):73-76.
16. Palmieri B, DMG, Noera G, Aspiro AM. Sorveglianza immunologica e immunoterapia aspecifica nel malato neoplastico. *Recenti progressi in medicina, il pensiero scientifico editore Roma*. 1976;61(6):824-880.
17. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol*. 2002; 169(3):1535-1541.
18. Kalis C, Gumenscheimer M, Freudenberg N, et al. Requirement for TLR9 in the immunomodulatory activity of Propionibacterium acnes. *J Immunol*. 2005;174(7):4295-4300.
19. Gambero M, Teixeira D, Butin L, et al. Propionibacterium acnes induces an adjuvant effect in B-1 cells and affects their phagocyte differentiation via a TLR2-mediated mechanism. *Immunobiology*. 2016; 221(9):1001-1011.
20. MacDonald AS, Straw AD, Bauman B, Pearce EJ. CD8- dendritic cell activation status plays an integral role in influencing Th2 response development. *J Immunol*. 2001;167(4):1982-1988.
21. Cervi L, MacDonald AS, Kane C, Dzierszinski F, Pearce EJ. Cutting edge: dendritic cells copulsed with microbial and helminth antigens undergo modified maturation, segregate the antigens to distinct intracellular compartments, and concurrently induce microbe-specific Th1 and helminth-specific Th2 responses. *J Immunol*. 2004;172(4):2016-2020.
22. Geniteau M, Quero AM, German A. Effect of Corynebacterium parvum on various viral infections in the mouse. *Ann Pharm Fr*. 1977; 35(5-6):181-187.
23. Glasgow LA, Fischbach J, Bryant SM, Kern ER. Immunomodulation of host resistance to experimental viral infections in mice: effects of

Corynebacterium acnes, Corynebacterium parvum, and Bacille calmette-guerin. *J Infect Dis*. 1977;135(5):763-770.
24. Kirchner H, Scott MT, Hirt HM, Munk K. Protection of mice against viral infection by Corynebacterium parvum and Bordetella pertussis. *J Gen Virol*. 1978;41(1):97-104.
25. Szmigielski S, JM. Reaction of cell-mediated immunity tolocal hyperthermia of tumors. *Cancers Ther Hypertherm Radiat*. 1978;1:80-88.
26. Szmigielski S, Kobus M, Gil J, Jeljaszewicz J, Pulverer G. Protection and therapy of mice with acute and chronic experimental virus infections with propionibacterium granulosum kp-45. *Zentralbl Bakteriol A*. 1980;248(3):286-295.
27. Papaevangelou G, Sparros L, Vissoulis C, et al. The effect of intradermal administration of corynebacterium parvum on the immune response to hepatitis Bs antigen. *J Med Virol*. 1977;1(1):15-19.
28. Kobus M, Luczak M, Sobiczewska E, Szmigielski S, Jeljaszewicz J, Pulverer G. Protection and therapy of experimental herpesvirus infections in mice with immunomodulating Propionibacterium avidum KP-40 and/or acyclovir. *Zentralbl Bakteriol*. 1997;285(3):445-449.
29. Teixeira D, Ishimura ME, Apostólico JS, et al. Propionibacterium acnes enhances the Immunogenicity of HIVBr18 human immunodeficiency virus-1 vaccine. *Front Immunol*. 2018;9:177.
30. Molife R, Hancock BW. Adjuvant therapy of malignant melanoma. *Crit Rev Oncol Hematol*. 2002;44(1):81-102.
31. Shepherd FA. Alternatives to chemotherapy and radiotherapy as adjuvant treatment for lung cancer. *Lung Cancer*. 1997;17(Suppl 1): S121-S136.
32. Budzko DB, Casals J, Waksman BH. Enhanced resistance against Junin virus infection induced by Corynebacterium parvum. *Infect Immun*. 1978;19(3):893-897.
33. Naficy K, Nategh R, Malekian M. Antiviral properties of five strains of Corynebacterium. *Prog Immunobiol Stand*. 1971;5:294-301.
34. Cerutti I. The antiviral properties of Corynebacterium parvum. *C R Acad Hebd Seances Acad Sci D*. 1974;279(11):963-966.
35. Schindler L, Streissle G, Kirchner H. Protection of mice against mouse hepatitis virus by Corynebacterium parvum. *Infect Immun*. 1981;32(3): 1128-1131.
36. Belyavsky M, Belyavskaya E, Levy GA, Leibowitz JL. Coronavirus MHV-3-induced apoptosis in macrophages. *Virology*. 1998;250(1):41-49.
37. Mak NK, Schiltknecht E, Ada GL. Protection of mice against influenza virus infection: enhancement of nonspecific cellular responses by Corynebacterium parvum. *Cell Immunol*. 1983;78(2):314-325.
38. Zgórniak-Nowosielska I, Cwik D, Sławińska B. Protection of mice against vaccinia and herpes simplex virus infection by Propionibacterium acnes. *Arch Immunol Ther Exp (Warsz)*. 1989;37(3-4):431-442.
39. Kounoue E, Nagafuchi S, Nakamura M, et al. Encephalomyocarditis (EMC) virus-induced diabetes mellitus prevented by Corynebacterium parvum in mice. *Experientia*. 1987;43(4):430-431.
40. Cohen DA, Morris RE, Bubel HC. Abortive ectromelia virus infection in peritoneal macrophages activated by Corynebacterium parvum. *J Leukoc Biol*. 1984;35(2):179-192.
41. Mayr A, Butnner M, Pawlas S, et al. Vergleichende Untersuchungen über die immunstimulierende (paramunisierende) Wirksamkeit von BCG, Levamisol, Corynebacterium parvum und Präparaten aus Pockenviren in verschiedenen "in vivo"-und "in vitro"-Testen. *J Vet Med, Series B*. 1986;33:321–339.
42. Weiss RC, Cox NR, Oostrom-Ram T. Effect of interferon or Propionibacterium acnes on the course of experimentally induced feline infectious peritonitis in specific-pathogen-free and random-source cats. *Am J Vet Res*. 1990;51(5):726-733.
43. Hall H, Teuscher C, Urie P, Boden B, Robison R. Induced regression of bovine papillomas by intralesional immunotherapy. *Ther Immunol*. 1994;1(6):319-324.
44. Flaminio MJ, Rush BR, Shuman W. Immunologic function in horses after non-specific immunostimulant administration. *Vet Immunol Immunopathol*. 1998;63(4):303-315.
45. Megid J, Dias JJG, Aguiar DM, Nardi Silva WB, Ribeiro MG,. Tratamento da Papillomatose Canina com Propionibacterium acnes. *Arquivo Brasileiro de Medicina Veterinária e Zootecnia*. 2001;53:574-576.
46. Megid J, Cremonini DN, Leomil H. Distribution of rabies virus in infected mice, vaccinated and submitted to P. acnes as immunomodulator. *Comp Immunol Microbiol Infect Dis*. 2002;25(4):237-248.
47. Megid J, Kaneno R. Natural killer activity in mice infected with rabies virus and submitted to P. acnes (Propionibacterium acnes) as immunomodulator. *Comp Immunol Microbiol Infect Dis*. 2000;23(2):91-97.
48. Megid J, Appolinario CM, Mazzini AM, Almeida MF. Evaluation of cytokines concentration and percentage of survival of rabies virus-infected mice submitted to anti-rabies Vero-cell propagated vaccine and P. acnes. *Vet Immunol Immunopathol*. 2006;114(1-2):192-196.
49. Davis EG, Rush BR, Blecha F. Increases in cytokine and antimicrobial peptide gene expression in horses by immunomodulation with Propionibacterium acnes. *Vet Ther*. 2003;4(1):5-11.
50. Caney S. Antiviral therapy in cats: current rationale and recommendations. *Clin Pract*. 2005;27:454-457.
51. Paillot R. A systematic review of the immune-modulators Parapoxvirus ovis and Propionibacterium acnes for the prevention of respiratory disease and other infections in the horse. *Vet Immunol Immunopathol*. 2013;153(1-2):1-9.
52. Vail CD, Nestved AJ, Rollins JB, et al. Adjunct treatment of equine respiratory disease complex (ERDC) with the propionibacterium acnes, immunostimulant, EqStim®. *J Equine Vet Sci*. 1990;10(6): 399-403.
53. Adams AA, Elzinga S, Lyman J, Little J. Effects of an immunostimulant containing Propionibacterium acnes (EqStim) on cell-mediated immunity and nasal shedding of respiratory pathogens using a model of "weaning" stress in foals. *J Equine Vet Sci*. 2016;38:72-81.
54. Nasser N. Treatment of common warts with the immune stimulant Propionium bacterium parvum. *An Bras Dermatol*. 2012;87:585-589.
55. Palmieri B, Bondi VM, Cermelli M. Propionibacterium acnes: a putative immunemodulating weapon against the coronavirus impending epidemy. *Int J Innov Sci Res Technol*. 2020;5(2):431-440.
56. Zhang Z, Wang FS. Plasmacytoid dendritic cells act as the most competent cell type in linking antiviral innate and adaptive immune responses. *Cell Mol Immunol*. 2005;2(6):411-417.
57. Marschner A, Rothenfusser S, Hornung V, et al. CpG ODN enhance antigen-specific NKT cell activation via plasmacytoid dendritic cells. *Eur J Immunol*. 2005;35(8):2347-2357.
58. Tanghetti EA. The role of inflammation in the pathology of acne. *J Clin Aesthet Dermatol*. 2013;6(9):27-35.
59. Aubin GG, Baud'huin M, Lavigne JP, et al. Interaction of Cutibacterium (formerly Propionibacterium) acnes with bone cells: a step toward understanding bone and joint infection development. *Sci Rep*. 2017;7:42918.
60. Mak TN, Fischer N, Laube B, et al. Propionibacterium acnes host cell tropism contributes to vimentin-mediated invasion and induction of inflammation. *Cell Microbiol*. 2012;14(11):1720-1733.
61. Du N, Cong H, Tian H, et al. Cell surface vimentin is an attachment receptor for enterovirus 71. *J Virol*. 2014;88(10):5816-5833.
62. Yu YT, Chien SC, Chen IY, et al. Surface vimentin is critical for the cell entry of SARS-CoV. *J Biomed Sci*. 2016;23:14.
63. Guo Y-R, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. *Mil Med Res*. 2020;7(1):11.
64. Stevens C, Henderson P, Nimmo ER, et al. The intermediate filament protein, vimentin, is a regulator of NOD2 activity. *Gut*. 2013;62(5): 695-707.
65. dos Santos G, Rogel MR, Baker MA, et al. Vimentin regulates activation of the NLRP3 inflammasome. *Nat Commun*. 2015;6:6574.
66. Thiagarajan PS, Yakubenko VP, Elsori DH, et al. Vimentin is an endogenous ligand for the pattern recognition receptor Dectin-1. *Cardiovasc Res*. 2013;99(3):494-504.

67. de Rivero Vaccari JP, Minkiewicz J, Wang X, et al. Astrogliosis involves activation of retinoic acid-inducible gene-like signaling in the innate immune response after spinal cord injury. *GLIA*. 2012;60(3):414-421.
68. Mostowy S, Shenoy AR. The cytoskeleton in cell-autonomous immunity: structural determinants of host defence. *Nat Rev Immunol*. 2015;15(9):559-573.

How to cite this article: Palmieri B, Vadalà M, Roncati L, et al. The long-standing history of *Corynebacterium parvum*, immunity, and virsuses. *J Med Virol*. 2020;92:2429–2439. https://doi.org/10.1002/jmv.26100